WEST Search History

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DATE: Tuesday, September 05, 2006

Hide?	Set Name	Query	Hit Count
	DB=PGPB,USPT; PLUR=YES; OP=OR		
☐	L4	L2 and (kidney or renal)	8850
☐	L3	L2 and kidney or renal	56108
☐	L2	L1 and (ACEI or ACE inhibitor)	15973
☐	L1	osteogenic adj protein or bone adj morphogenic adj protein or bone adj morphogenetic adj protein or op or bmp	69417

END OF SEARCH HISTORY

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 NEWS  1           Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2           "Ask CAS" for self-help around the clock
 NEWS  3  FEB 27   New STN AnaVist pricing effective March 1, 2006
 NEWS  4  MAY 10   CA/CAplus enhanced with 1900-1906 U.S. patent records
 NEWS  5  MAY 11   KOREAPAT updates resume
 NEWS  6  MAY 19   Derwent World Patents Index to be reloaded and enhanced
 NEWS  7  MAY 30   IPC 8 Rolled-up Core codes added to CA/CAplus and
                   USPATFULL/USPAT2
 NEWS  8  MAY 30   The F-Term thesaurus is now available in CA/CAplus
 NEWS  9  JUN 02   The first reclassification of IPC codes now complete in
                   INPADOC
 NEWS 10  JUN 26   TULSA/TULSA2 reloaded and enhanced with new search and
                   and display fields
 NEWS 11  JUN 28   Price changes in full-text patent databases EPFULL and PCTFULL
 NEWS 12  JUl 11   CHEMSAFE reloaded and enhanced
 NEWS 13  JUl 14   FSTA enhanced with Japanese patents
 NEWS 14  JUl 19   Coverage of Research Disclosure reinstated in DWPI
 NEWS 15  AUG 09   INSPEC enhanced with 1898-1968 archive
 NEWS 16  AUG 28   ADISCTI Reloaded and Enhanced
 NEWS 17  AUG 30   CA(SM)/CAplus(SM) Austrian patent law changes

 NEWS EXPRESS  JUNE 30 CURRENT WINDOWS VERSION IS V8.01b, CURRENT
               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 26 JUNE 2006.

 NEWS HOURS    STN Operating Hours Plus Help Desk Availability
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 NEWS IPC8     For general information regarding STN implementation of IPC 8
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FILE 'HOME' ENTERED AT 13:42:16 ON 05 SEP 2006

=> file medline
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.21       0.21
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FILE 'MEDLINE' ENTERED AT 13:42:36 ON 05 SEP 2006

 FILE LAST UPDATED: 2 Sep 2006 (20060902/UP).  FILE COVERS 1950 TO DATE.

 On December 11, 2005, the 2006 MeSH terms were loaded.

 The MEDLINE reload for 2006 is now (26 Feb.) available.  For details
 on the 2006 reload, enter HELP RLOAD at an arrow prompt (=>).
 See also:

    http://www.nlm.nih.gov/mesh/
    http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html
    http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_med_data_changes.html
    http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_2006_MeSH.html

 OLDMEDLINE is covered back to 1950.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2006 vocabulary.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> tu OP or BMP or osteogenic(w)protein or bone(w)morphogenic(w)protein or
bone(w)morphogenetic(w)protein
TU IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> s tu OP or BMP or osteogenic(w)protein or bone(w)morphogenic(w)protein or
bone(w)morphogenetic(w)protein
       1240985 TU
           219 TUS
       1241162 TU
                 (TU OR TUS)
          8619 OP
          1068 OPS
          9272 OP
                 (OP OR OPS)
             0 TU OP
                 (TU(W)OP)
          4863 BMP
          1554 BMPS
          5222 BMP
                 (BMP OR BMPS)
          7082 OSTEOGENIC
             1 OSTEOGENICS
          7082 OSTEOGENIC
                 (OSTEOGENIC OR OSTEOGENICS)
       1565590 PROTEIN
       1313769 PROTEINS
       1985822 PROTEIN
                 (PROTEIN OR PROTEINS)
           349 OSTEOGENIC(W)PROTEIN
        474158 BONE
         96660 BONES
        493178 BONE
                 (BONE OR BONES)
          1153 MORPHOGENIC
             3 MORPHOGENICS
          1155 MORPHOGENIC
                 (MORPHOGENIC OR MORPHOGENICS)
       1565590 PROTEIN
```

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       1313769 PROTEINS
       1985822 PROTEIN
                 (PROTEIN OR PROTEINS)
           324 BONE(W)MORPHOGENIC(W)PROTEIN
        474158 BONE
         96660 BONES
        493178 BONE
                 (BONE OR BONES)
         11946 MORPHOGENETIC
             5 MORPHOGENETICS
         11951 MORPHOGENETIC
                 (MORPHOGENETIC OR MORPHOGENETICS)
       1565590 PROTEIN
       1313769 PROTEINS
       1985822 PROTEIN
                 (PROTEIN OR PROTEINS)
          7251 BONE(W)MORPHOGENETIC(W)PROTEIN
L1        8297 TU OP OR BMP OR OSTEOGENIC(W)PROTEIN OR BONE(W)MORPHOGENIC(W)PRO
               TEIN OR BONE(W)MORPHOGENETIC(W)PROTEIN

=> s l1 and ace(w)inhibitor or acei
         18167 ACE
           149 ACES
         18247 ACE
                 (ACE OR ACES)
        282789 INHIBITOR
        573245 INHIBITORS
        701381 INHIBITOR
                 (INHIBITOR OR INHIBITORS)
         10727 ACE(W)INHIBITOR
          1153 ACEI
           323 ACEIS
          1295 ACEI
                 (ACEI OR ACEIS)
L2        1296 L1 AND ACE(W)INHIBITOR OR ACEI

=> s l2 and renal or kidney
        363790 RENAL
            23 RENALS
        363798 RENAL
                 (RENAL OR RENALS)
        495205 KIDNEY
         56551 KIDNEYS
        508302 KIDNEY
                 (KIDNEY OR KIDNEYS)
L3      508446 L2 AND RENAL OR KIDNEY

=> s l2 and (renal or kidney)
        363790 RENAL
            23 RENALS
        363798 RENAL
                 (RENAL OR RENALS)
        495205 KIDNEY
         56551 KIDNEYS
        508302 KIDNEY
                 (KIDNEY OR KIDNEYS)
L4         535 L2 AND (RENAL OR KIDNEY)

=> s l2 and enalapril or catopril or fonsinopril or trandolopril or alacepril or
moveltorpil or quinaprilat or moexipril or peronodpril or pentopril or ancovenin or
phenacein or nicotianamin
          5933 ENALAPRIL
             5 CATOPRIL
             0 FONSINOPRIL
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             1 TRANDOLOPRIL
            78 ALACEPRIL
             0 MOVELTORPIL
           117 QUINAPRILAT
            71 MOEXIPRIL
             0 PERONODPRIL
            15 PENTOPRIL
             2 ANCOVENIN
             3 PHENACEIN
             0 NICOTIANAMIN
L5         493 L2 AND ENALAPRIL OR CATOPRIL OR FONSINOPRIL OR TRANDOLOPRIL OR
               ALACEPRIL OR MOVELTORPIL OR QUINAPRILAT OR MOEXIPRIL OR PERONODP
              RIL OR PENTOPRIL OR ANCOVENIN OR PHENACEIN OR NICOTIANAMIN

=> s l5 and (renal or kidney)
        363790 RENAL
            23 RENALS
        363798 RENAL
                 (RENAL OR RENALS)
        495205 KIDNEY
         56551 KIDNEYS
        508302 KIDNEY
                 (KIDNEY OR KIDNEYS)
L6         166 L5 AND (RENAL OR KIDNEY)

=> dis his

     (FILE 'HOME' ENTERED AT 13:42:16 ON 05 SEP 2006)

     FILE 'MEDLINE' ENTERED AT 13:42:36 ON 05 SEP 2006
L1        8297 S TU OP OR BMP OR OSTEOGENIC(W)PROTEIN OR BONE(W)MORPHOGENIC(W)
L2        1296 S L1 AND ACE(W)INHIBITOR OR ACEI
L3      508446 S L2 AND RENAL OR KIDNEY
L4         535 S L2 AND (RENAL OR KIDNEY)
L5         493 S L2 AND ENALAPRIL OR CATOPRIL OR FONSINOPRIL OR TRANDOLOPRIL O
L6         166 S L5 AND (RENAL OR KIDNEY)

=> dup rem l6
PROCESSING COMPLETED FOR L6
L7         166 DUP REM L6 (0 DUPLICATES REMOVED)

=> dis ibib abs l6 150-166

L6   ANSWER 150 OF 166     MEDLINE on STN
ACCESSION NUMBER:    90039676     MEDLINE
DOCUMENT NUMBER:     PubMed ID: 2553899
TITLE:               Comparative studies of tissue inhibition by angiotensin
                     converting enzyme inhibitors.
AUTHOR:              Johnston C I; Fabris B; Yamada H; Mendelsohn F A; Cubela R;
                     Sivell D; Jackson B
CORPORATE SOURCE:    Department of Medicine, Melbourne University, Austin
                     hospital, Heidelberg, Victoria, Australia.
SOURCE:              Journal of hypertension. Supplement : official journal of
                     the International Society of Hypertension, (1989 Sep) Vol.
                     7, No. 5, pp. S11-6.  Ref: 23
                     Journal code: 8501422. ISSN: 0952-1178.
PUB. COUNTRY:        ENGLAND: United Kingdom
DOCUMENT TYPE:       Journal; Article; (JOURNAL ARTICLE)
                     General Review; (REVIEW)
LANGUAGE:            English
FILE SEGMENT:        Priority Journals
ENTRY MONTH:         198912
ENTRY DATE:          Entered STN: 28 Mar 1990
                     Last Updated on STN: 28 Mar 1990
```

Entered Medline: 19 Dec 1989

AB There is increasing evidence that inhibition of tissue angiotensin converting enzyme (ACE) is important for the pharmacokinetics and pharmacodynamic effects of ACE inhibitors. Radioligand inhibitor binding methods using 125I-351A and either tissue homogenates or in vitro autoradiography have allowed in vitro and ex vivo quantitation of tissue ACE inhibition by a variety of ACE inhibitors. The rank order of potency against plasma as well as lung, kidney, and cardiac homogenates was quinaprilat = benazeprilat greater than perindoprilat greater than lisinopril greater than enalaprilat greater than fosinoprilat. The highest concentration of ACE in the heart was found in the cardiac valves followed by the right and left atria, then the right and left ventricles. Ex vivo studies showed that after oral administration of quinapril, ACE was inhibited dose-dependently in the lung, kidney, aorta and heart for more than 24h. Tissue bioavailability of the inhibitor is also an important determinant of tissue ACE inhibition. Perindopril crossed the blood-brain barrier and inhibited brain ACE at high doses, but after equivalent doses of quinapril no brain ACE inhibition could be demonstrated. These results suggest that it may be possible to design ACE inhibitors to have specific effects on ACE in different tissues.

L6 ANSWER 151 OF 166 MEDLINE on STN
ACCESSION NUMBER: 89306037 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2545470
TITLE: The effects of nephrectomy and angiotensin converting enzyme inhibitor on production and clearance rates of angiotensinogen in dogs.
AUTHOR: Toyozaki N; Ito T
CORPORATE SOURCE: Japan Self-Defense Forces Central Hospital, Tokyo.
SOURCE: Nippon Naibunpi Gakkai zasshi, (1989 Feb 20) Vol. 65, No. 2, pp. 128-35.
Journal code: 0413717. ISSN: 0029-0661.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198908
ENTRY DATE: Entered STN: 9 Mar 1990
Last Updated on STN: 9 Mar 1990
Entered Medline: 17 Aug 1989

AB The clearance and production rates of plasma angiotensinogen of normal dog, nephrectomized dog and angiotensin converting enzyme inhibitor (ACEI) administered dog were calculated. Plasma angiotensinogen was measured by adding excessive dog renin to the plasma sample. The clearance rate was 4.4, 4.0 and 3.8 ml/kg/hr and the production rate was 9.6, 21.6 and 7.6 micrograms/kg/hr, respectively. After nephrectomy, the clearance rate of angiotensinogen decreased only 10 percent but the production rate increased more than twice. These results mean that the kidney does not play an important role in the clearance of angiotensinogen but has some influence on its production. This increase in production rate due to nephrectomy may mean that the kidney has some inhibitory effect on the secretion of angiotensinogen from the liver but this phenomenon is not able to explain by much less hydrolysis of angiotensinogen. By the administration of ACEI, not only the clearance rate but also the production rate of plasma angiotensinogen decreased as compared with control dog, but the balance between them resulted in the decreased plasma angiotensinogen concentration. These results show that the decreased production rate was greater than the decreased clearance rate in ACEI administered dog.

L6 ANSWER 152 OF 166 MEDLINE on STN
ACCESSION NUMBER: 89283960 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2734717

TITLE: [Renal insufficiency and treatment of persistent cardiac insufficiency with converting enzyme inhibitor]. Insuffisance renale et traitement de l'insuffisance cardiaque refractaire par inhibiteur de l'enzyme de conversion.
AUTHOR: Chamontin B; Begasse F; Salva P; Salvador M
SOURCE: Therapie, (1989 Jan-Feb) Vol. 44, No. 1, pp. 29-32. Journal code: 0420544. ISSN: 0040-5957.
PUB. COUNTRY: France
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: French
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198907
ENTRY DATE: Entered STN: 9 Mar 1990
Last Updated on STN: 9 Mar 1990
Entered Medline: 25 Jul 1989

AB The purpose of this retrospective study was to consider impaired renal function in patients with severe congestive heart failure after converting enzyme inhibition and to emphasize the characteristics of this population. The study concerned 26 patients (pts), 72.5 +/- 8.1 years old, with a severe congestive heart failure (NYHA Class IV). Before treatment serum creatinine was slightly increased and the introduction of angiotensin converting enzyme inhibitor (ACEI) - Captopril 58.9 +/- 17.3 mg/j or enalapril 9.2 +/- 4.4 mg - impaired renal function from 132.0 +/- 50.7 mumol/l to 183.5 +/- 139.3 mumol/l (n = 26; p less than 0.05). Patients were separated in 3 groups: in group I; 15 pts, serum creatinine remained unchanged under ACEI in despite of the significant decrease of blood pressure (BP); from 140.7 +/- 24.0/82.5 +/- 13.4 to 120.3 +/- 12.8/71.8 +/- 8.7 mmHg (p less than 0.01). The cause of heart failure was an ischemic heart disease (IHD) in 15 patients (chi 2 test, p less than 0.05), a dilated cardiomyopathy in 4 pts and an aortic or mitral valvular regurgitation in 2 pts. In contrast renal function was significantly impaired in group II; serum creatinine increased from 120.8 +/- 25.2 to 189.0 +/- 80.7 mumol/l under ACEI. BP remained unchanged 136.9 +/- 29.0/78.1 +/- 4.9 and 118.7 +/- 13.6/75.6 +/- 7.6 mmHg respectively before and after treatment. There was 4 pts with dilated cardiomyopathy, 4 pts with mitral or aortic valvular regurgitation and only one with IHD. The introduction of an ACEI in two pts--group III--with severe tricuspid regurgitation induced an acute and reversal renal failure (serum creatinine at 600 mumol/l).

L6 ANSWER 153 OF 166 MEDLINE on STN
ACCESSION NUMBER: 89205941 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2539761
TITLE: Quinapril--a preclinical review of the pharmacology, pharmacokinetics, and toxicology.
AUTHOR: Kaplan H R; Taylor D G; Olson S C; Andrews L K
CORPORATE SOURCE: Parke-Davis Pharmaceutical Research Division, Warner-Lambert Company, Ann Arbor, Michigan.
SOURCE: Angiology, (1989 Apr) Vol. 40, No. 4 Pt 2, pp. 335-50. Ref: 12
Journal code: 0203706. ISSN: 0003-3197.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198905
ENTRY DATE: Entered STN: 6 Mar 1990
Last Updated on STN: 6 Mar 1990
Entered Medline: 18 May 1989

AB Quinapril is an orally active, non-peptide, nonsulfhydryl angiotensin-converting enzyme (ACE) inhibitor that acts potently and

specifically to interrupt the conversion of angiotensin I to angiotensin II in both plasma and tissue. Quinapril is enzymatically hydrolyzed to a pharmacologically active diacid form quinaprilat. Quinapril is efficacious in hypertensive models exhibiting both high (renal hypertensive rats, diuretic-treated dogs) and normal (spontaneously hypertensive rats) plasma renin activity. Quinapril does not prevent the development of hypertension when plasma renin activity (PRA) is markedly suppressed as in the deoxycorticosterone-saline treated rat. Hemodynamic studies in dogs indicate that quinapril decreases total peripheral and renal vascular resistance. Quinaprilat produces natriuresis and mild diuresis at doses that do not alter mean arterial blood pressure. Quinapril has the potential to affect plasma lipids beneficially or at least be "lipid neutral." Oral absorption of quinapril is rapid in rats, dogs, and monkeys. There is rapid and extensive distribution of radiolabel to most tissues except brain. Plasma radiolabel concentration-time profiles exhibit polyexponential decay with a prolonged terminal phase at low concentrations in all species. Metabolism to compounds other than quinaprilat is not extensive. Quinapril is excreted primarily as quinaprilat and to a lesser degree as quinapril. Quinapril is well tolerated in a variety of pharmacologic safety screens and its toxicity profile is similar to that of other ACE inhibitors. Quinapril does not adversely affect reproduction; it is not teratogenic, carcinogenic, or mutagenic.(ABSTRACT TRUNCATED AT 250 WORDS)

L6 ANSWER 154 OF 166 MEDLINE on STN
ACCESSION NUMBER: 89099115 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2905468
TITLE: Synergistic renal effects of RS-10085, an ace inhibitor, and fenoldopam, a DA1 agonist, in the rat.
AUTHOR: McClelland D L; Rosenkranz R P
CORPORATE SOURCE: Institute of Pharmacology, Syntex Research, Palo Alto, California 94304.
SOURCE: Proceedings of the Western Pharmacology Society, (1988) Vol. 31, pp. 87-90.
Journal code: 7505899. ISSN: 0083-8969.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198902
ENTRY DATE: Entered STN: 8 Mar 1990
Last Updated on STN: 6 Feb 1995
Entered Medline: 23 Feb 1989

L6 ANSWER 155 OF 166 MEDLINE on STN
ACCESSION NUMBER: 88270819 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3391004
TITLE: Effect of renal impairment on disposition of pentopril and its active metabolite.
AUTHOR: Rakhit A; Radensky P; Szerlip H M; Kochak G M; Audet P R; Hurley M E; Feldman G M
CORPORATE SOURCE: Pharmaceuticals Division, Ciba-Geigy Corp., Summit, NJ 07901.
SOURCE: Clinical pharmacology and therapeutics, (1988 Jul) Vol. 44, No. 1, pp. 39-48.
Journal code: 0372741. ISSN: 0009-9236.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198808
ENTRY DATE: Entered STN: 8 Mar 1990
Last Updated on STN: 8 Mar 1990

Entered Medline: 24 Aug 1988

AB Disposition of pentopril was studied in 15 male volunteers with varying renal functions. Mild to moderate compromise in renal function did not demonstrate any appreciable changes in plasma concentration of pentopril, the prodrug ester of the active angiotensin-converting enzyme (ACE) inhibitor CGS 13934. This is consistent with the known elimination pattern for pentopril, which is eliminated primarily by hydrolysis to the active inhibitor. In contrast, the plasma concentration of the active ACE inhibitor was sensitive to moderate changes in renal function. Because of the reciprocal relationship of AUC and clearance, AUC did not change to any appreciable extent until creatinine clearance (CLCR) dropped to about 50 ml/min. Below 50 ml/min of CLCR, AUC and half-life increased sharply with reduced kidney function. Because of the significant contribution of the renal secretion process to total renal elimination of both pentopril and the active metabolite, prediction of renal clearance from CLCR was poor at relatively normal kidney function (CLCR greater than 80 ml/min). However, renal secretory clearances for both pentopril and metabolite were well correlated to p-aminohippuric acid clearance. In patients with moderately compromised renal function (glomerular filtration rate less than 40 ml/min), tubular secretion rate of creatinine approaches its glomerular filtration rate and hence CLCR could be used as a predictor of renal clearance and other disposition parameters. Plasma ACE activity also demonstrated prolonged inhibition with decreased renal function. Based on the prolonged blockade of plasma ACE activity, some correction in dose or dosing interval is anticipated in patients with moderately compromised renal function (CLCR less than 50 ml/min).

L6 ANSWER 156 OF 166 MEDLINE on STN

ACCESSION NUMBER: 88024666 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2822067
TITLE: Pharmacokinetics of pentopril in the elderly.
AUTHOR: Rakhit A; Kochak G M; Tipnis V; Radensky P; Hurley M E; Williams R
CORPORATE SOURCE: Pharmaceuticals Division CIBA-GEIGY Corporation, Ardsley, NY.
SOURCE: British journal of clinical pharmacology, (1987 Sep) Vol. 24, No. 3, pp. 351-7.
Journal code: 7503323. ISSN: 0306-5251.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198711
ENTRY DATE: Entered STN: 5 Mar 1990
Last Updated on STN: 5 Mar 1990
Entered Medline: 30 Nov 1987

AB 1 The pharmacokinetics of pentopril in elderly subjects aged 70 to 75 years were compared with those of healthy young subjects aged 22 to 26 years. 2 There were no appreciable differences between the two groups in any of the pharmacokinetic parameters for pentopril derived from its plasma data (Cmax, tmax, AUC and t1/2). 3 In contrast, the active metabolite CGS 13934 exhibited an increase in mean values of AUC by 56% in elderly compared to young. However, the difference was not statistically significant (0.1 greater than P greater than 0.05). The variability was, however, significantly higher (P less than 0.05) in the elderly group compared with young. The peak time for metabolite was also significantly delayed in elderly (3.9 vs 2.5 h). The mean half-life for metabolite however, was comparable for the two groups (3.6 vs 3.9 h). 4 Urinary analysis showed a significant decrease in renal clearance (CLR) with age for both pentopril (107 vs 203 ml min-1) and its active metabolite (116 vs 205 ml min-1). 5 Pharmacodynamic measurements of the

renin-angiotensin system, in general, demonstrated a drug effect at 2 h with recovery almost to the basal value at 24 h except for plasma ACE activity at 24 h in the elderly. 6 Because of large variability and an increase in the mean AUC of active metabolite in elderly, greater caution may be necessary for dose selection in this group. However, no substantial difference in extent of drug accumulation is anticipated in elderly compared with young people based on the similarity in t1/2 values.

L6 ANSWER 157 OF 166 MEDLINE on STN
ACCESSION NUMBER: 87274222 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3038424
TITLE: Role of renin-angiotensin and kallikrein-kinin systems on the mechanism of the hypotensive effects of converting enzyme inhibitor, alacepril.
AUTHOR: Tanaka S; Shimamoto K; Ando T; Nakahashi Y; Ura N; Hosoda S; Ishida H; Yamaji I; Yokoyama T; Masuda A; +
SOURCE: Clinical and experimental hypertension. Part A, Theory and practice, (1987) Vol. 9, No. 2-3, pp. 605-9.
Journal code: 8207790. ISSN: 0730-0077.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198708
ENTRY DATE: Entered STN: 5 Mar 1990
Last Updated on STN: 3 Mar 2000
Entered Medline: 28 Aug 1987
AB In four patients with essential hypertension and one patient with renovascular hypertension, decreases in blood pressure and plasma angiotensin II levels, and increases in plasma renin activity and plasma kinin levels were observed during eight days of alacepril treatment. Significant correlations between the changes in mean arterial pressure and those in plasma angiotensin II or kinin levels were observed positively or negatively, respectively, in the essential hypertensives. These findings suggest that the hypotensive effect of alacepril might be caused mainly by a decrease in plasma angiotensin II levels and, at least in part, by an increase in plasma kinin levels.

L6 ANSWER 158 OF 166 MEDLINE on STN
ACCESSION NUMBER: 87188592 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3032491
TITLE: Inhibition of renal clearance of furosemide by pentopril, an angiotensin-converting enzyme inhibitor.
AUTHOR: Rakhit A; Kochak G M; Tipnis V; Hurley M E
SOURCE: Clinical pharmacology and therapeutics, (1987 May) Vol. 41, No. 5, pp. 580-6.
Journal code: 0372741. ISSN: 0009-9236.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198706
ENTRY DATE: Entered STN: 3 Mar 1990
Last Updated on STN: 3 Feb 1997
Entered Medline: 22 Jun 1987
AB The pharmacokinetic interaction between pentopril (250 mg) and furosemide (40 mg) was studied in 12 normal healthy volunteers after oral administration of each drug alone and in combination. No significant changes in any pharmacokinetic parameters of pentopril or its active metabolite (CGS 13934) were observed on coadministration of furosemide. In contrast, pentopril induced significant changes in disposition of furosemide. Pentopril decreased renal clearance (CLR) of furosemide by 54% and the fraction excreted unchanged

in urine also decreased by 55%. However, such decrease in CLR of furosemide was compensated by a simultaneous increase in glucuronidation (by 200%), resulting in a slight increase in systemic clearance (decreased AUC). Systemic bioavailability of furosemide appears to be unchanged in the presence of pentopril (0.46 vs. 0.41). No effect of pentopril on plasma protein binding of furosemide was detected. In spite of the decreased CLR and urinary excretion rate of furosemide, the urinary output (1749 vs. 1774 ml/6 hr) and Na+ excretion (757 vs. 816 mEq/6 hr) remained almost unchanged. These findings suggest that total furosemide (unchanged and glucuronide) might contribute to diuresis and natriuresis rather than the unchanged furosemide alone. Because of unchanged pharmacodynamic effect, such pharmacokinetic interaction may not require any dosage adjustment for furosemide on pentopril coadministration.

L6 ANSWER 159 OF 166 MEDLINE on STN
ACCESSION NUMBER: 86159004 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3006712
TITLE: Effect of alacepril on renin-angiotensin-aldosterone system and kallikrein-kinin-prostaglandin system in experimental animals.
AUTHOR: Hosoki K; Takeyama K; Minato H; Fukuya F; Kawahara S; Kadokawa T
SOURCE: Arzneimittel-Forschung, (1986) Vol. 36, No. 1, pp. 77-83. Journal code: 0372660. ISSN: 0004-4172.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198604
ENTRY DATE: Entered STN: 21 Mar 1990
Last Updated on STN: 3 Mar 2000
Entered Medline: 21 Apr 1986

AB The effects of 1-[(S)-3-acetylthio-2-methylpropanoyl]-L-prolyl-L-phenylalanine (alacepril, DU-1219), an orally active angiotensin converting enzyme (ACE) inhibitor, on humoral factors which participated in the blood pressure control were examined with various experimental animals. In conscious renal hypertensive dogs, alacepril (3 mg/kg p.o.) showed decreases in plasma ACE activity and plasma aldosterone concentration, and increases in plasma renin activity and plasma angiotensin I concentration accompanied by a significant reduction in blood pressure. In conscious normotensive dogs, alacepril (1 and 3 mg/kg p.o.) showed an increase in urinary excretion of bradykinin accompanied by increases in urinary water and sodium excretion. In spontaneously hypertensive rats, alacepril (30 and 100 mg/kg p.o.) showed increases in urinary excretion of bradykinin and 6-keto-prostaglandin Fl alpha, and a decrease in that of aldosterone accompanied by increased in excretion of water and sodium. These results indicate that the antihypertensive activity of alacepril is due to the suppression of renin-angiotensin-aldosterone system and the enhancement of kallikrein-kinin-prostaglandin system through the inhibition of ACE (kininase II) activity in vivo.

L6 ANSWER 160 OF 166 MEDLINE on STN
ACCESSION NUMBER: 86159002 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3513779
TITLE: Effect of the novel orally active angiotensin converting enzyme inhibitor alacepril on cardiovascular system in experimental animals.
AUTHOR: Takeyama K; Minato H; Nakatsuji K; Suzuki H; Nose I; Oka M; Hosoki K; Hatano N; Kadokawa T
SOURCE: Arzneimittel-Forschung, (1986) Vol. 36, No. 1, pp. 69-73. Journal code: 0372660. ISSN: 0004-4172.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198604
ENTRY DATE: Entered STN: 21 Mar 1990
Last Updated on STN: 21 Mar 1990
Entered Medline: 21 Apr 1986

AB Effects of 1-[(S)-3-acetylthio-2-methylpropanoyl]-L-prolyl-L-phenylalanine (alacepril, DU-1219) a new orally active angiotensin converting enzyme (ACE) inhibitor, on cardiovascular system in experimental animals were examined. In conscious renal hypertensive dogs, alacepril (3 mg/kg p.o.) caused a marked reduction in systolic and diastolic blood pressure (SBP and DBP) and total peripheral vascular resistance (TPR), but did not change significantly heart rate (HR), cardiac output (CO), stroke volume (SV), cardiac work (CW) and electrocardiogram (ECG). Captopril (3 mg/kg, p.o.) showed similar changes in cardiovascular parameters as alacepril. In anesthetized open-chest normotensive dogs, alacepril (3-100 micrograms/kg/min for 10 min, i.v. infusion) tended to decrease DBP and TPR, but did not change significantly CO, stroke work (SW), left ventricular end diastolic pressure (LVEDP), dp/dt and HR. Captopril also showed similar effects but these changes were greater in extent than those of alacepril. In conscious renal hypertensive rats, alacepril did not affect the regional cerebral blood flow in the frontal cortex and the dorsal hippocampus after single (3 and 10 mg/kg) and successive (3 mg/kg/d for 7 days) oral administration. Captopril (10 mg/kg) significantly decreased blood flow in the frontal cortex after single oral administration. In conscious normotensive dogs, alacepril (3 and 30 mg/kg p.o.) increased renal plasma flow (RPF), urine volume (UV), urinary sodium excretion (UNaV) and urinary Na+/k+ ratio, but did not change glomerular filtration rate (GFR) and urinary potassium excretion (UKV). Captopril (3 and 30 mg/kg p.o.) also showed similar changes as alacepril. These effects of alacepril on cardiovascular system resemble those of captopril and might be considered as a favourable profile for the antihypertensive agent.

L6 ANSWER 161 OF 166 MEDLINE on STN
ACCESSION NUMBER: 86159000 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3513777
TITLE: General pharmacology of the novel angiotensin converting enzyme inhibitor alacepril. 1st communication: Effects on cardiovascular, visceral and renal functions and on blood.
AUTHOR: Matsuno Y; Taira N; Fujitani B; Ito T; Kadokawa T
SOURCE: Arzneimittel-Forschung, (1986) Vol. 36, No. 1, pp. 55-62. Journal code: 0372660. ISSN: 0004-4172.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198604
ENTRY DATE: Entered STN: 21 Mar 1990
Last Updated on STN: 21 Mar 1990
Entered Medline: 21 Apr 1986

AB The effects of 1-[(S)-3-acetylthio-2-methylpropanoyl]-L-prolyl-L-phenylalanine (alacepril, DU-1219) an antihypertensive compound with angiotensin converting enzyme inhibitory activity, and its metabolite, desacetyl-alacepril (DU-1227), on the cardiovascular and autonomic nervous systems and on the blood were compared with those of captopril in the experimental animals. Alacepril and DU-1227 at the i.v. dose of 10 mg/kg gradually lowered the diastolic blood pressure in pentobarbital anesthetized dogs. Captopril showed similar effects. However, the former two compounds showed triphasic effects on the carotid blood flow, i.e., transient increase immediately after the injection,

second increase 2 min later, and gradual decrease 20-30 min later. The second increase by DU-1227 was more potent than that by alacepril . Alacepril, DU-1227 and captopril did not affect the pressor responses induced by norepinephrine in anesthetized cats. The contractions of the nictitating membrane in cats induced by electrical stimulation of the cervical sympathetic nerve or epinephrine were depressed with high doses of these three compounds. Captopril potentiated the contractions induced by bradykinin in isolated guinea-pig ileum, while alacepril and DU-1227 were without effect. These three compounds neither affected the resting tension of isolated ileum in guinea-pigs and rabbits nor the contractions induced by acetylcholine, histamine, serotonin and nicotine of isolated guinea-pig ileum. Alacepril at the oral dose of 60 mg/kg decreased the total acidity in pylorus ligated rats, and at higher doses depressed the intestinal charcoal meal passage in mice. Alacepril at comparatively low doses decreased the urine volume with slight reduction of Na+ and K+ excretions in saline-loaded rats.(ABSTRACT TRUNCATED AT 250 WORDS)

L6 ANSWER 162 OF 166 MEDLINE on STN
ACCESSION NUMBER: 86158999 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3006711
TITLE: Metabolism of protein conjugate of desacetyl-alacepril and its effect on angiotensin converting enzyme in renal hypertensive rats.
AUTHOR: Matsumoto K; Nambu K; Fujii T; Takeyama K; Miyazaki H; Hashimoto M
SOURCE: Arzneimittel-Forschung, (1986) Vol. 36, No. 1, pp. 52-4. Journal code: 0372660. ISSN: 0004-4172.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198604
ENTRY DATE: Entered STN: 21 Mar 1990
Last Updated on STN: 21 Mar 1990
Entered Medline: 21 Apr 1986

AB The fate of protein conjugate of desacetyl-alacepril (DU-1227) and its effect on angiotensin I converting enzyme (ACE) activity in renal hypertensive rats were studied. [14C]DU-1227-protein conjugate was prepared by ultrafiltration method and administered intravenously in rats. Elimination of radioactivity of [14C]DU-1227-protein from plasma after injection seemed much slower than that reported of [14C]alacepril (1-[(S)-3-acetylthio-2-methylpropanoyl]-L-prolyl-L-phenylalanine, DU-1219) given orally. In the plasma unbound fraction, captopril and captopril-cysteine were detected. Most tissue levels were higher than plasma levels. Significant reduction of tissue ACE activity was seen after administration of the conjugate. Radioactivity was mostly excreted in feces. Captopril, captopril disulfide and captopril-cysteine were found as urinary metabolites. These findings indicate that protein-bound DU-1227 readily dissociated and released DU-1227 was converted to captopril in vivo and can therefore participate in prolonged hypotensive effect exerted by alacepril .

L6 ANSWER 163 OF 166 MEDLINE on STN
ACCESSION NUMBER: 86158998 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3006710
TITLE: Tissue levels, tissue angiotensin converting enzyme inhibition and antihypertensive effect of the novel antihypertensive agent alacepril in renal hypertensive rats.
AUTHOR: Nambu K; Matsumoto K; Takeyama K; Hosoki K; Miyazaki H; Hashimoto M
SOURCE: Arzneimittel-Forschung, (1986) Vol. 36, No. 1, pp. 47-51.

Journal code: 0372660. ISSN: 0004-4172.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198604
ENTRY DATE: Entered STN: 21 Mar 1990
Last Updated on STN: 21 Mar 1990
Entered Medline: 21 Apr 1986

AB Tissue levels, tissue angiotensin I converting enzyme (ACE) inhibition and hypotension were examined 20 min, 1, 5 and 14 h after oral administration of 1-[(S)-3-acetylthio-2-methylpropanoyl]-L-prolyl-L-phenylalanine (alacepril, DU-1219) (37.5 mg (92 mumol)/kg) or 1-[(S)-3-mercapto-2-methylpropanoyl]-L-proline (captopril) (20.0 mg (92 mumol)/kg) in renal hypertensive rats, using 14C-labeled compounds. Alacepril exerted a more gradual and more sustained antihypertensive effect than captopril. The maximal hypotension was observed 1 and 5 h after administration of captopril and alacepril , respectively. After administration of [14C]captopril, serum level reached the maximum at 20 min and then decreased rapidly. After administration of [14C]alacepril, serum level reached the maximum at 1 h and decreased more slowly than after [14C]captopril. Time course patterns of tissue levels were essentially in parallel with those of serum levels. Captopril exerted the maximal reduction of ACE activity in tissues 20 min after oral administration and thereafter, the reduction was diminished with time rapidly. [14C]Alacepril showed gradual reduction (the maximum at 1 h) and recovery of ACE activity relative to captopril. After oral administration of [14C]alacepril, tissue unbound fractions contained captopril and its derived metabolites while serum unbound fraction contained the intermediate metabolite desacetyl-alacepril (DU-1227) as well. Correlations between ACE inhibition and tissue levels and between changes in tissue ACE inhibition and in blood pressure with time after oral administration of the two agents were discussed. Furthermore, the direct comparison of alacepril and captopril was attempted by the difference in blood pressures and in ACE inhibitions induced after oral administration of the agents.

L6 ANSWER 164 OF 166 MEDLINE on STN
ACCESSION NUMBER: 86158997 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3513776
TITLE: Disposition and metabolism of the novel antihypertensive agent alacepril in rats.
AUTHOR: Matsumoto K; Miyazaki H; Fujii T; Yoshida K; Amejima H; Hashimoto M
SOURCE: Arzneimittel-Forschung, (1986) Vol. 36, No. 1, pp. 40-6.
Journal code: 0372660. ISSN: 0004-4172.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198604
ENTRY DATE: Entered STN: 21 Mar 1990
Last Updated on STN: 21 Mar 1990
Entered Medline: 21 Apr 1986

AB Disposition and metabolism of 1-[(S)-3-acetylthio-2-methylpropanoyl]-L-prolyl-L-phenylalanine (alacepril, DU-1219) in rats were studied and compared to those of 1-[(S)-3-mercapto-2-methylpropanoyl]-L-proline (captopril), using 14C-labeled compounds. Some tissue homogenates and plasma of rats were incubated in vitro with [14C]alacepril or [14C]captopril at the concentration of 50 nmol/ml. For in vivo studies, radioactive agents were orally or intravenously administered to rats in doses of 46 mumol/kg (18.7 and 10 mg/kg for alacepril and captopril, respectively) or 460 mumol/kg. In vitro studies revealed that [14C]alacepril is converted to captopril via desacetyl-

alacepril (DU-1227) in the liver, kidney and intestine homogenates, but not in the lung homogenate and plasma where deacetylation alone occurred. DU-1227 and captopril formed were found to be partly bound with endogenous -SH compounds i.e. cysteine, glutathione and probably, protein. 1 h after oral administration of [14C]alacepril , plasma levels of total radioactivity reached a maximum of 8 nmol/ml and disappeared with t1/2 of 2.6 h. [14C]Captopril radioactivity was maximum (13 nmol/ml) at 40 min with the disappearance t1/2 of 1.9 h. Similarly to total radioactivity, levels of radioactivity unbound and bound to plasma protein after [14C]alacepril were lower at maximum and disappeared more slowly than those after [14C]captopril. After oral administration of [14C]alacepril, DU-1227, captopril and mixed disulfides of captopril with cysteine and glutathione were detected in the plasma unbound fraction. The three metabolites except for DU-1227 were commonly detected after [14C]captopril.(ABSTRACT TRUNCATED AT 250 WORDS)

L6 ANSWER 165 OF 166 MEDLINE on STN
ACCESSION NUMBER: 86077087 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3000389
TITLE: Antihypertensive activity of alacepril, an orally active angiotensin converting enzyme inhibitor, in renal hypertensive rats and dogs.
AUTHOR: Takeyama K; Minato H; Fukuya F; Kawahara S; Hosoki K; Kadokawa T
SOURCE: Arzneimittel-Forschung, (1985) Vol. 35, No. 10, pp. 1502-7. Journal code: 0372660. ISSN: 0004-4172.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198601
ENTRY DATE: Entered STN: 21 Mar 1990
Last Updated on STN: 21 Mar 1990
Entered Medline: 17 Jan 1986

AB Alacepril (1-[(S)-3-acetylthio-2-methylpropanoyl]-L-prolyl-L-phenylalanine, DU-1219) showed a dose related and long lasting antihypertensive effect in renal hypertensive rats (two-kidney, one-clip), a typical renin dependent hypertensive model. The maximum hypotensive potency of alacepril (1-30 mg/kg) after single oral administration was slightly weaker than that of captopril (1-30 mg/kg). Judging from the AOC (area over the antihypertensive curve) value, the overall antihypertensive activity of alacepril was 3 times more potent than that of captopril on a weight basis. The long lasting antihypertensive effect of alacepril in renal hypertensive rats was also confirmed by once daily successive oral administration (1-2 mg/kg/d). In renal hypertensive dogs, alacepril (3 mg/kg) showed a stable and sustained hypotensive effect, and its duration of action was longer than that of captopril. Although alacepril did not possess a significant in vitro angiotensin converting enzyme (ACE) inhibitory activity, orally given alacepril (5.6-56.1 mg/kg) produced a potent and prolonged in vivo ACE inhibition which was estimated by suppression on angiotensin-I (310 ng/kg i.v.) induced pressor response in conscious normotensive rats. The prolonged in vivo ACE inhibitory activity of alacepril (5.6 mg/kg) was also observed in conscious normotensive dogs. These results suggest that the disposition and metabolism of orally given alacepril are responsible for the prolonged ACE inhibition and, concomitantly, for exerting the long lasting antihypertensive effect. Consequently, alacepril is a novel orally active ACE inhibitor having a potent and prolonged antihypertensive activity, and these properties suggest that alacepril is favorable for the treatment of hypertension.

L6 ANSWER 166 OF 166 MEDLINE on STN

ACCESSION NUMBER: 85053381 MEDLINE
DOCUMENT NUMBER: PubMed ID: 6094343
TITLE: Influence of captopril and enalapril on regional vascular alpha-adrenergic receptor reactivity in SHR.
AUTHOR: Richer C; Doussau M P; Giudicelli J F
SOURCE: Hypertension, (1984 Sep-Oct) Vol. 6, No. 5, pp. 666-74. Journal code: 7906255. ISSN: 0194-911X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198412
ENTRY DATE: Entered STN: 20 Mar 1990
Last Updated on STN: 3 Feb 1997
Entered Medline: 31 Dec 1984

AB The effects of short-term oral treatment with captopril and enalapril (two angiotensin-I-converting-enzyme inhibitors [ACEIs] that were administered in equipotent antihypertensive doses) on the systemic vasopressor response and on the renal, mesenteric, and hindlimb vascular responses to cirazoline and UK-14,304 (alpha 1- and alpha 2-adrenergic receptor-specific agonists, respectively) were investigated in adult pithed spontaneously hypertensive rats (SHR) of the Okamoto-Aoki strain. In the nonbinephrectomized animal, captopril and enalapril reduced to the same extent the systemic blood pressure and renal and hindlimb vascular resistances. They also decreased to the same extent systemic pressor and regional vasoconstrictor responses to cirazoline and UK-14,304, especially in the renal and mesenteric vascular beds. Simultaneously, the effects of angiotensin I and angiotensin II on the pressor response were abolished and almost not modified. In the binephrectomized animals, captopril and enalapril no longer reduced the systemic blood pressure and regional vascular resistances, but whereas the sympathoinhibitory effect of captopril vs the systemic pressor and regional vasoconstrictor responses to cirazoline and UK-14,304 persisted, those of enalapril disappeared.(ABSTRACT TRUNCATED AT 250 WORDS)

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L6 ANSWER 140 OF 166 MEDLINE on STN
ACCESSION NUMBER: 91107827 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2273086
TITLE: Pharmacokinetics of quinapril and its active metabolite quinaprilat during continuous ambulatory peritoneal dialysis.
AUTHOR: Swartz R D; Starmann B; Horvath A M; Olson S C; Posvar E L
CORPORATE SOURCE: Department of Internal Medicine, University of Michigan Medical Center, Ann Arbor 48109-0364.
SOURCE: Journal of clinical pharmacology, (1990 Dec) Vol. 30, No. 12, pp. 1136-41. Journal code: 0366372. ISSN: 0091-2700.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199102
ENTRY DATE: Entered STN: 29 Mar 1991
Last Updated on STN: 29 Mar 1991
Entered Medline: 22 Feb 1991

AB The pharmacokinetics of quinapril, a novel angiotensin converting enzyme (ACE) inhibitor, and its active metabolite, quinaprilat, were determined following a single 20-mg oral dose of quinapril in six patients with chronic renal failure maintained on continuous ambulatory peritoneal dialysis (CAPD). Overall, quinapril was well tolerated by

these CAPD patients, with mild and transient side effects, not unexpected in this clinical setting, which included pruritus, headache, nausea, and cough. Blood pressure reduction was observed in four of six patients, with onset reliably two to four hours after dosing and duration up to 48 hours, associated with quinaprilat concentrations in plasma above 90 ng/mL for at least 33 hours postdose. Two patients experienced significant hypotension, systolic blood pressure below 90 mm Hg, which responded promptly to oral fluid administration and/or reduction in dialysate tonicity. The pharmacokinetic profile of quinapril in these CAPD patients was not significantly different from that previously observed in healthy subjects with normal renal function and in patients with moderate to severe renal dysfunction not yet requiring dialysis (RDND). The apparent elimination half-life of quinapril was approximately one hour, with negligible dialysate excretion. The pharmacokinetic profile of quinaprilat in these CAPD patients was similar to that previously observed in patients with RDND. The elimination half-life of quinaprilat was markedly prolonged when compared to that in healthy subjects and averaged 20 hours, with only a small amount of quinaprilat excreted in dialysate (mean = 2.6% of total dose).(ABSTRACT TRUNCATED AT 250 WORDS)

L6 ANSWER 141 OF 166 MEDLINE on STN
ACCESSION NUMBER: 91036119 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2229454
TITLE: Pharmacokinetics of quinapril and its active metabolite, quinaprilat, in patients on chronic hemodialysis.
AUTHOR: Blum R A; Olson S C; Kohli R K; Horvath A M; Sedman A J; Posvar E L
CORPORATE SOURCE: Clinical Pharmacokinetics Laboratory, Millard Fillmore Hospital, Buffalo, NY 14209.
SOURCE: Journal of clinical pharmacology, (1990 Oct) Vol. 30, No. 10, pp. 938-42.
Journal code: 0366372. ISSN: 0091-2700.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199012
ENTRY DATE: Entered STN: 8 Feb 1991
Last Updated on STN: 8 Feb 1991
Entered Medline: 7 Dec 1990

AB The pharmacokinetics of quinapril and its active metabolite, quinaprilat, were evaluated in 12 patients with end-stage renal disease (ESRD) on chronic hemodialysis. Each subject received a single 20-mg oral dose of quinapril 4 hours before a 4-hour hemodialysis treatment. Serial dialysate and blood samples were obtained over 4 and 96 hours, respectively. Samples were analyzed for quinapril and quinaprilat concentrations by gas chromatography. Mean tmax and Cmax values for quinapril were 1.2 hours and 129 ng/mL, respectively. Only one patient had detectable quinapril dialysate concentrations which accounted for 2.8% of the quinapril dose. Mean apparent plasma clearance for quinapril was 1275 mL/min with a mean half-life of 1.7 hours. Quinapril was extensively de-esterified to its diacid metabolite, quinaprilat. Mean tmax and Cmax for quinaprilat were 4.5 hours and 671 ng/mL, respectively. Mean apparent plasma clearance for quinaprilat was 24.0 mL/min with a mean half-life of 17.5 hours. As with quinapril, quinaprilat was not readily dialyzable. Only 5.4% of the administered quinapril dose was recovered as quinaprilat during a single hemodialysis treatment. In view of these results, supplemental quinapril doses need not be routinely given to patients following hemodialysis. Overall, quinapril and quinaprilat pharmacokinetics in patients with ESRD on chronic hemodialysis were not markedly different from those previously observed in patients with moderate to severe renal dysfunction (CLcr less

than 29 mL/min) not yet requiring hemodialysis (RDND).

L6 ANSWER 142 OF 166 MEDLINE on STN
ACCESSION NUMBER: 91031081 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2226219
TITLE: Angiotensin converting enzyme inhibitors and moderate hypertension.
AUTHOR: McAreavey D; Robertson J I
CORPORATE SOURCE: Department of Cardiology, Western General Hospital, Edinburgh, Scotland.
SOURCE: Drugs, (1990 Sep) Vol. 40, No. 3, pp. 326-45. Ref: 208
Journal code: 7600076. ISSN: 0012-6667.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199012
ENTRY DATE: Entered STN: 8 Feb 1991
Last Updated on STN: 8 Feb 1991
Entered Medline: 24 Dec 1990

AB Recently there has been extensive development of orally active angiotensin converting enzyme (ACE) inhibitors in addition to those already marketed, for example, captopril, enalapril, lisinopril and ramipril. It was initially thought that ACE inhibitors were likely to be most useful as antihypertensive agents in conditions in which circulating renin and angiotensin II were elevated. However, it is now clear that they can also lower arterial pressure when plasma renin is not high. In addition, they have beneficial effects in cardiac failure. Thus, captopril, enalapril, lisinopril and ramipril can be used in the treatment of mild to moderate hypertension either alone or in conjunction with diuretics or calcium antagonists. Broadly speaking, efficacy appears to be similar to that of beta-blockers or diuretics. Unfortunately, however, there are no long term studies comparing one ACE inhibitor with another or with other classes of antihypertensive agents. Furthermore, there are no prognostic studies which show that use of ACE inhibitors reduces morbidity or mortality in hypertension. Many new ACE inhibitors are undergoing clinical assessment, including alacepril, cilazapril, fosenopril, perindopril, quinapril and ramipril. The drugs vary, in that some exist in the active form whereas others are prodrugs which are converted to the active agent following absorption. In addition they each possess one of several ligands, for example, carboxyl, phosphinyl or sulfhydryl groups, and so vary in their affinity for ACE. Although many of these agents are renally excreted, a small number are metabolised via the liver (e.g. quinapril and spirapril) and this may prove advantageous in the presence of renal impairment. In common with captopril and enalapril, the new ACE inhibitors inhibit the renin-angiotensin system and initial results suggest that they are effective in lowering blood pressure in essential hypertension. Furthermore, they reduce systemic vascular resistance in the absence of a reflex tachycardia. There are a number of adverse effects which are attributable to the pharmacological mechanism of the ACE inhibitors as a group; these include hypotension, particularly in patients with high renin levels, prior diuretic use, renal impairment or in the elderly. Additional adverse effects may relate to chemical structure. The high incidence of adverse effects noted in early studies related to excess dosage and to the presence of a sulfhydryl group, which the more recently developed ACE inhibitors lack. The adverse effects most commonly reported with established and new ACE inhibitors include headache and fatigue, cough, skin rashes, hypotension and diarrhoea. As a group, ACE inhibitors have an acceptable but not negligible adverse effect burden. (ABSTRACT TRUNCATED AT 400 WORDS)

L6 ANSWER 143 OF 166 MEDLINE on STN
ACCESSION NUMBER: 91001406 MEDLINE

DOCUMENT NUMBER: PubMed ID: 2144994
TITLE: The pharmacokinetics and pharmacodynamics of quinapril and quinaprilat in renal impairment.
AUTHOR: Begg E J; Robson R A; Bailey R R; Lynn K L; Frank G J; Olson S C
CORPORATE SOURCE: Department of Clinical Pharmacology, Christchurch School of Medicine, New Zealand.
SOURCE: British journal of clinical pharmacology, (1990 Aug) Vol. 30, No. 2, pp. 213-20.
Journal code: 7503323. ISSN: 0306-5251.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199011
ENTRY DATE: Entered STN: 17 Jan 1991
Last Updated on STN: 17 Jan 1991
Entered Medline: 21 Nov 1990

AB 1. The pharmacokinetics and pharmacodynamics of quinapril and its active metabolite quinaprilat were studied in 20 subjects with renal function varying from normal to severe renal failure, during the approach to and at steady-state, and for 72 h after cessation of quinapril 20 mg orally for 7 days. 2. The apparent oral plasma clearance of quinaprilat (dose of quinapril equivalent/AUC of quinaprilat) was directly related to creatinine clearance (CLCr). The predicted apparent oral clearance of quinaprilat was zero when CLCr was zero, suggesting minimal extrarenal elimination. 3. Peak and trough concentrations of quinaprilat, and its apparent elimination half-life, varied inversely with CLCr. 4. Trough concentrations of quinaprilat showed no accumulation between 2 and 7 days, even in severe renal impairment. 5. There was a weak relationship between the oral plasma clearance of quinapril and CLCr. 6. ACE inhibition was marked and prolonged in all subjects, with 50% inhibition at 2.7 +/- 1.9% ng ml-1 of quinaprilat. The time for which ACE inhibition was greater than 90% was related inversely to CLCr. 7. Aldosterone concentrations and plasma renin activity responded in a predictable way, but with no clear relationship To CLCr. 8. Atrial natriuretic peptide concentrations were not affected by quinapril administration. 9. Glomerular filtration rate, as measured by Tc99mDTPA clearance, was not affected by quinapril administration. 10. Blood pressure at steady-state decreased significantly in the subjects with hypertension. The changes in blood pressure were not related to renal function. 11. These results suggest that the dosage rate of quinapril may have to be altered in renal impairment.(ABSTRACT TRUNCATED AT 250 WORDS)

L6 ANSWER 144 OF 166 MEDLINE on STN
ACCESSION NUMBER: 90367385 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2203579
TITLE: Clinical pharmacokinetics of the newer ACE inhibitors. A review.
AUTHOR: Kelly J G; O'Malley K
CORPORATE SOURCE: Institute of Biopharmaceutics, Monksland, Athlone, Ireland.
SOURCE: Clinical pharmacokinetics, (1990 Sep) Vol. 19, No. 3, pp. 177-96. Ref: 119
Journal code: 7606849. ISSN: 0312-5963.
PUB. COUNTRY: New Zealand
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199010
ENTRY DATE: Entered STN: 9 Nov 1990
Last Updated on STN: 9 Nov 1990

Entered Medline: 11 Oct 1990

AB The orally active angiotensin-converting inhibitors (ACE inhibitors) such as captopril and enalapril represent a significant therapeutic advance in the treatment of hypertension and congestive heart failure. Enalapril differs from captopril in several respects. It is a prodrug converted by hepatic esterolysis to the active (but more poorly absorbed) diacid, enalaprilat. Enalaprilat is more potent than captopril, more slowly eliminated and does not possess a sulfhydryl (SH) group. Enalapril was rapidly followed by a number of newer ACE inhibitors, the majority of which are similar to enalapril in that they are prodrugs, converted by hepatic esterolysis to a major active but poorly absorbed diacid metabolite. In one case (delapril) there are 2 active metabolites; in another (alacepril) the prodrug is converted in vivo to captopril. Lisinopril is an exception in that it is an enalaprilat-like diacid but with acceptable oral bioavailability, so that the prodrug route is not employed. The newer ACE inhibitors are at widely different stages of development, and it is not yet clear how many will reach regular clinical use. Of these newer drugs, lisinopril is the longest established and is the subject of the widest published literature. For a number there is as yet little published pharmacokinetic information. A variety of assay methods have been employed to characterise the pharmacokinetics of the ACE inhibitors, including enzymatic techniques, radioimmunoassay and chromatography. The peak plasma concentrations of the prodrugs are generally observed at around 1 hour and those of the diacid metabolites at about 2 to 4 hours. However, there is considerable variation within and between drugs, with benazepril and benazeprilat reaching peak concentrations early and enalapril and enalaprilat typical of later times to peak. Absorption of the active diacids is generally poor, and moderate (typically 30 to 70%) for the prodrugs. The bioavailability of lisinopril is about 25%. It is difficult to talk meaningfully about half-lives of the active drugs. The declines in their plasma concentrations are polyphasic and, if analytical sensitivity allows, active drug may be found at 48 hours or more following administration. This may reflect binding to ACE in plasma. Half-lives of accumulation are of the order of 12 hours; protein binding varies from little (lisinopril) to 90% (benazeprilat). Elimination is mostly renal but there may be biliary elimination for some, such as benazeprilat and fosinopril. The half-lives of the prodrugs are short. Impaired renal function decreases the elimination rate of the diacids.(ABSTRACT TRUNCATED AT 400 WORDS)

L6 ANSWER 145 OF 166 MEDLINE on STN

ACCESSION NUMBER:	90268845 MEDLINE
DOCUMENT NUMBER:	PubMed ID: 2189623
TITLE:	Quinapril: overview of preclinical data.
AUTHOR:	Kaplan H R; Taylor D G; Olson S C
CORPORATE SOURCE:	Parke-Davis Pharmaceutical Research Division, Warner-Lambert Company, Ann Arbor, Michigan 48105.
SOURCE:	Clinical cardiology, (1990 Jun) Vol. 13, No. 6 Suppl 7, pp. VII6-12. Ref: 14 Journal code: 7903272. ISSN: 0160-9289.
PUB. COUNTRY:	United States
DOCUMENT TYPE:	Journal; Article; (JOURNAL ARTICLE) General Review; (REVIEW)
LANGUAGE:	English
FILE SEGMENT:	Priority Journals
ENTRY MONTH:	199007
ENTRY DATE:	Entered STN: 10 Aug 1990 Last Updated on STN: 10 Aug 1990 Entered Medline: 9 Jul 1990

AB Quinapril hydrochloride, a new, orally active, nonpeptide, nonsulfhydryl angiotensin-converting enzyme (ACE) inhibitor, has been studied extensively in a variety of in vitro and in vivo animal models. Quinapril inhibits the contractile and pressor effects of angiotensin I in rabbit aorta and in rats, respectively, and lowers blood pressure in both high-

and normal-renin rodent and diuretic-treated dog models of hypertension. No tolerance to the antihypertensive effects of quinapril was noted in spontaneously hypertensive rats treated with quinapril for up to 14 consecutive days. As with other ACE inhibitors, quinapril had virtually no effect on the development of hypertension in the renin-independent one-kidney deoxycorticosterone (DOCA)-salt hypertensive rat. Antihypertensive activity best correlates with the inhibition of tissue (vascular) ACE, and thus the reduction in peripheral vascular resistance associated with plasma and tissue ACE most likely accounts for the therapeutic benefit of quinapril. Preliminary data from a trial of quinapril in cardiomyopathic hamsters show that the drug prevents the anticipated decline in left ventricular contractile function and retards the temporal progression of left ventricular failure. ACE inhibitors have been found to have a lipid-neutral profile, unlike some other classes of antihypertensives. Quinapril is rapidly absorbed and extensively distributed to all tissues except brain. It is rapidly hydrolyzed to quinaprilat, its pharmacologically active diacid form. Metabolism to other compounds is not extensive. Quinapril's preclinical toxicologic profile is similar to that of other ACE inhibitors. Long-term toxicology studies show that quinapril is not teratogenic, carcinogenic, or mutagenic.

L6 ANSWER 146 OF 166 MEDLINE on STN
ACCESSION NUMBER: 90250721 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2187090
TITLE: The value of the captopril test and the effect of captopril on renal function.
AUTHOR: Lu Z W; Liu L S
CORPORATE SOURCE: Cardiovascular Institute, Chinese Academy of Medical Science, Beijing.
SOURCE: Journal of human hypertension, (1990 Apr) Vol. 4, No. 2, pp. 138-40.
Journal code: 8811625. ISSN: 0950-9240.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199006
ENTRY DATE: Entered STN: 20 Jul 1990
Last Updated on STN: 20 Jul 1990
Entered Medline: 21 Jun 1990

AB We have investigated the use of captopril as a screening test for renovascular hypertension and compared the effects of captopril on renal function in patients with renovascular hypertension and those without renovascular hypertension. The captopril test and kidney gamma scintigraphy were carried out in 50 hypertensive patients, 13 with renovascular hypertension and 37 without. Blood samples were drawn for the determination of plasma renin activity and kidney gamma scintigraphy was done before and 60 minutes after 50 mg oral captopril administration. Results suggesting the diagnosis of renovascular hypertension are the following: a basal and stimulated plasma renin activity of 4 ng ml/hr or more and an absolute increase in plasma renin activity of 3 ng/ml/hr or more if basal plasma renin activity was less than 4 ng/ml/hr. Data from kidney gamma scintigraphy showed that captopril causes a decrease in clearance rate at 20 minutes in patients with renovascular hypertension but not in patients without renovascular hypertension. We conclude that the captopril test can be used to screen for renovascular hypertension, but catopril may impair the renovascular hypertensive patient's renal function.

L6 ANSWER 147 OF 166 MEDLINE on STN
ACCESSION NUMBER: 90219897 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1691408
TITLE: The management of hypertension in older patients.

AUTHOR: Schnaper H W
CORPORATE SOURCE: Center for Aging, University of Alabama, Birmingham 35294.
SOURCE: Journal of cardiovascular pharmacology, (1990) Vol. 15 Suppl 2, pp. S56-61.
Journal code: 7902492. ISSN: 0160-2446.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199005
ENTRY DATE: Entered STN: 22 Jun 1990
Last Updated on STN: 29 Jan 1996
Entered Medline: 15 May 1990

AB Hypertension need not be a natural consequence of aging; nevertheless, as many as 70% of individuals aged 70 years or more have diastolic blood pressures greater than or equal to 90 mm Hg and/or systolic blood pressures greater than 160 mm Hg. Well-controlled trials have documented significant reductions in cardiovascular mortality with treatment of diastolic elevation. Double-blind, long-term, open-label studies have been conducted of quinapril, a new angiotensin-converting enzyme (ACE) inhibitor, in 451 older patients compared with 1,887 younger patients. Results of these studies showed that quinapril is equally effective in older and younger patients. The studies also demonstrated that the safety of quinapril in the treatment of older patients is comparable with that in younger patients, in terms of both the incidence of adverse events and the types of adverse events reported. However, because many older patients have impaired renal function, which can prolong the half-life of renally excreted ACE inhibitors such as quinaprilat (the active metabolite of quinapril), they should be started on lower doses of quinapril (5 mg) than are used in younger patients. The shorter half-life and duration of action of quinaprilat compared with other once-daily ACE inhibitors may make quinapril better suited than these other agents for use in older patients.

L6 ANSWER 148 OF 166 MEDLINE on STN
ACCESSION NUMBER: 90102078 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2532450
TITLE: Significance of kallikrein-kinin and renin-angiotensin systems in the hypotensive mechanism of angiotensin-I converting enzyme inhibitors in essential hypertensives.
AUTHOR: Iimura O; Shimamoto K
CORPORATE SOURCE: Second Department of Internal Medicine, Sapporo Medical College, Japan.
SOURCE: Advances in experimental medicine and biology, (1989) Vol. 247A, pp. 39-48.
Journal code: 0121103. ISSN: 0065-2598.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199002
ENTRY DATE: Entered STN: 28 Mar 1990
Last Updated on STN: 3 Mar 2000
Entered Medline: 2 Feb 1990

AB This study was undertaken to further clarify the role of kallikrein-kinin and renin-angiotensin systems in the hypotensive mechanisms of the angiotensin-I converting enzyme inhibitor by using highly sensitive and specific radioimmunoassays in patients with essential hypertension. Captopril was administered for 14 days (chronic effect), and the acute effects of captopril, alacepril and ramipril were also studied in the in-patients with essential hypertension. All of these converting enzyme inhibitors rapidly decreased the blood pressure and plasma angiotensin II levels, and increased plasma and urinary kinin and plasma renin activity in the acute effect. Following the administration of

captopril for 14 days, these decreases and increases were maintained. The change of blood pressure was significantly correlated negatively with that of plasma kinin levels and positively with that of plasma angiotensin II levels in both the acute and chronic effect of converting enzyme inhibitors. Urine volume and urinary sodium excretion were markedly augmented, while both the change of urine volume and that of urinary sodium excretion were negatively correlated with the change of blood pressure in the chronic effect. These findings suggest that the hypotensive effect of converting enzyme inhibitors might be caused by an increase of plasma kinin and a decrease of plasma angiotensin II, and in part by an augmentation of urine volume and urinary sodium excretion. In this drug treatment, the renal kallikrein-kinin system may also play some role in the increase of urine volume and urinary sodium excretion through the increased kinin in the kidney.

L6 ANSWER 149 OF 166 MEDLINE on STN
ACCESSION NUMBER: 90047741 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2554364
TITLE: Effect of captopril or enalapril on renal prostaglandin E2.
AUTHOR: Katayama S; Inaba M; Maruno Y; Omoto A; Itabashi A; Kawazu S; Ishii J
CORPORATE SOURCE: Fourth Department of Medicine, Saitama Medical School, Japan.
SOURCE: Prostaglandins, (1989 Oct) Vol. 38, No. 4, pp. 401-11. Journal code: 0320271. ISSN: 0090-6980.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198912
ENTRY DATE: Entered STN: 28 Mar 1990
Last Updated on STN: 28 Mar 1990
Entered Medline: 13 Dec 1989

AB Since one of the hypotensive mechanisms of angiotensin-converting enzyme inhibitor (ACEI) has been suggested to be mediated through the renal kinin-prostaglandin (PG) axis, the present study was designed to investigate the effect of captopril (C) or enalapril (E) on renal PGE2 excretion or synthesis. Wistar male rats (BW 200-250 g) were given orally captopril at 30 mg/kg/day or enalapril at 10 or 30 mg/kg for one week. Before and after ACEI, blood pressure (tail cuff method) as well as PRA and urinary PGE2 excretion was determined. Renopapillary slices were obtained from some of the rats including controls and incubated to determine PGE2 synthesis. C or E administration resulted in a blood pressure decrease of 21 to 36 mm Hg with an increase in PRA. Urine volume and sodium excretion increased after daily treatment with C or E at 30 mg/kg. Urinary PGE2 excretion increased 1.4-fold in response to C, but not to E. Papillary PGE2 synthesis demonstrated a marked decrease 2 h after in vivo administration of either ACEI compared to controls. However, when C or enalaprilat was added in vitro to renal slices obtained from controls, only C at 10(-5) M showed a significant 2-fold increase in renal PGE2 synthesis. These results suggest that (1) renal PGE2 synthesis may be dependent on circulating angiotensin II. (2) C, but not enalaprilat, has a direct stimulatory effect on renal PGE2 synthesis and (3) renal PGE2 may not be involved very much in the hypotensive effect of ACEI.

L6 ANSWER 150 OF 166 MEDLINE on STN
ACCESSION NUMBER: 90039676 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2553899
TITLE: Comparative studies of tissue inhibition by angiotensin converting enzyme inhibitors.
AUTHOR: Johnston C I; Fabris B; Yamada H; Mendelsohn F A; Cubela R;

Sivell D; Jackson B
CORPORATE SOURCE: Department of Medicine, Melbourne University, Austin hospital, Heidelberg, Victoria, Australia.
SOURCE: Journal of hypertension. Supplement : official journal of the International Society of Hypertension, (1989 Sep) Vol. 7, No. 5, pp. S11-6. Ref: 23
Journal code: 8501422. ISSN: 0952-1178.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198912
ENTRY DATE: Entered STN: 28 Mar 1990
Last Updated on STN: 28 Mar 1990
Entered Medline: 19 Dec 1989

AB There is increasing evidence that inhibition of tissue angiotensin converting enzyme (ACE) is important for the pharmacokinetics and pharmacodynamic effects of ACE inhibitors. Radioligand inhibitor binding methods using 125I-351A and either tissue homogenates or in vitro autoradiography have allowed in vitro and ex vivo quantitation of tissue ACE inhibition by a variety of ACE inhibitors. The rank order of potency against plasma as well as lung, kidney, and cardiac homogenates was quinaprilat = benazeprilat greater than perindoprilat greater than lisinopril greater than enalaprilat greater than fosinoprilat. The highest concentration of ACE in the heart was found in the cardiac valves followed by the right and left atria, then the right and left ventricles. Ex vivo studies showed that after oral administration of quinapril, ACE was inhibited dose-dependently in the lung, kidney, aorta and heart for more than 24h. Tissue bioavailability of the inhibitor is also an important determinant of tissue ACE inhibition. Perindopril crossed the blood-brain barrier and inhibited brain ACE at high doses, but after equivalent doses of quinapril no brain ACE inhibition could be demonstrated. These results suggest that it may be possible to design ACE inhibitors to have specific effects on ACE in different tissues.

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L6 ANSWER 130 OF 166 MEDLINE on STN
ACCESSION NUMBER: 92121278 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1770031
TITLE: Effects of angiotensin-converting enzyme inhibitor (alacepril) and calcium antagonist (nicardipine) in hypertensive non-insulin-dependent diabetic patients with microalbuminuria.
AUTHOR: Haisa S; Norii T; Takatori E; Goto A; Morioka S; Uchida K; Himei H
CORPORATE SOURCE: Okayama City General Hospital, Japan.
SOURCE: The Journal of diabetic complications, (1991 Apr-Sep) Vol. 5, No. 2-3, pp. 162-4.
Journal code: 8708656. ISSN: 0891-6632.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199202
ENTRY DATE: Entered STN: 15 Mar 1992
Last Updated on STN: 15 Mar 1992
Entered Medline: 21 Feb 1992

AB The influence of alacepril (50 mg/day) on arterial blood pressure and microproteinuria in 26 hypertensive non-insulin-dependent

diabetic patients was studied for 16 weeks. Alacepril reduced blood pressure gradually from 175/88 (standard error of mean [SEM] 2.6/1.7) to 152/81 (3.3/2.0) mm Hg (P less than .005) and albuminuria from 160.6 (SEM 29.1) to 98.1 (14.1) mg/g Cr (P less than .05), while serum blood urea nitrogen, creatinine, HbA1c, and fructosamine (FRA) remained stable. No significant changes occurred in the urinary beta 2 microglobulin and N-acetyl-beta-D-glucosaminidase levels. As compared with the effects of a calcium antagonist (nicardipine, 60 mg/day) that reduced blood pressure from 170/92 (SEM 2.5/1.4) to 154/84 (2.5/1.5) mm Hg (P less than .001) and albuminuria from 162.2 (SEM 33.9) to 95.4 (25.0) mg/g Cr (not significant), it is suggested that the angiotensin-converting enzyme inhibitor (alacepril) may have an advantageous renal effect in spite of its mild antihypertensive effect.

L6 ANSWER 131 OF 166 MEDLINE on STN
ACCESSION NUMBER: 92059553 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1951760
TITLE: Effects of central and intravascular angiotensin I and II on the choroid plexus.
AUTHOR: Maktabi M A; Heistad D D; Faraci F M
CORPORATE SOURCE: Department of Anesthesia, University of Iowa College of Medicine, Iowa City 52242.
CONTRACT NUMBER: HL-16066 (NHLBI)
HL-38901 (NHLBI)
NS-24621 (NINDS)
+
SOURCE: The American journal of physiology, (1991 Nov) Vol. 261, No. 5 Pt 2, pp. R1126-32.
Journal code: 0370511. ISSN: 0002-9513.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199112
ENTRY DATE: Entered STN: 24 Jan 1992
Last Updated on STN: 24 Jan 1992
Entered Medline: 23 Dec 1991

AB The choroid plexus contains receptors for angiotensin II (ANG II) and a very high concentration of angiotensin-converting enzyme. The goal of this study was to test the hypothesis that central, as well as circulating, ANG I and II decrease blood flow to the choroid plexus. Under control conditions in anesthetized rabbits, blood flow (microspheres) to the choroid plexus was 449 +/- 21 (mean +/- SE) ml.min-1.100 g(-1). Intravascular ANG I (30 and 100 ng.kg-1.min-1) decreased blood flow to the choroid plexus by 19 +/- 14 and 28 +/- 18%, respectively. Intravascular ANG II (30 and 100 ng.kg-1.min-1) also produced a decrease in blood flow by 28 +/- 9 and 47 +/- 7%, respectively. When administered into the lateral ventricle, ANG I and II (10 and 100 ng.kg-1.min-1) decreased blood flow to a similar degree: 22 +/- 11 and 31 +/- 10% and 12 +/- 10 and 27 +/- 8%, respectively. Cerebral blood flow was not decreased by intravascular or central ANG I or II. The angiotensin-converting enzyme inhibitor quinaprilat prevented the decrease in blood flow to the choroid plexus in response to ANG I without affecting responses to ANG II. Thus 1) circulating ANG I and II are potent constrictors of blood vessels of the choroid plexus, 2) the constrictor effect of ANG I on the blood vessels of the choroid plexus appears mediated primarily by generation of ANG II, and 3) intracerebroventricular ANG I produces large reductions in the blood flow to the choroid plexus, which suggests that there is an effective central system that converts ANG I to ANG II.(ABSTRACT TRUNCATED AT 250 WORDS)

L6 ANSWER 132 OF 166 MEDLINE on STN
ACCESSION NUMBER: 92046997 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1942767

TITLE: Cause of variable therapeutic efficiency of angiotensin converting enzyme inhibitor on glomerular lesions.
AUTHOR: Ikoma M; Kawamura T; Kakinuma Y; Fogo A; Ichikawa I
CORPORATE SOURCE: Department of Pediatrics, Vanderbilt University School of Medicine, Nashville, Tennessee.
CONTRACT NUMBER: DK 37868 (NIDDK)
SOURCE: Kidney international, (1991 Aug) Vol. 40, No. 2, pp. 195-202.
Journal code: 0323470. ISSN: 0085-2538.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199111
ENTRY DATE: Entered STN: 24 Jan 1992
Last Updated on STN: 24 Jan 1992
Entered Medline: 25 Nov 1991

AB We tested the effect of angiotensin I converting enzyme inhibitor (ACEI) on established glomerular sclerosis. Starting eight weeks after subtotal nephrectomy (sNPX), rats were given enalapril for four weeks in a dose of 50 (Group II, N = 5) or 200 mg/liter drinking water (Group III, N = 5). A third group of sNPX rats not given ACEI served as control (Group I, N = 10). Glomerular sclerosis index (SI, 0 to 4 scale) was assessed three-dimensionally on serial thin sections for individual glomeruli at biopsy (Bx, 8 weeks), and divided into four different ranks of severity and compared to autopsy (Ax, 12 weeks). In Group I control rats, 48% of the glomeruli at Bx had SI between 0 and 1 (rank 1, average: 0.49 +/- 0.06), 36% between 1 and 2 (rank 2, average: 1.53 +/- 0.06), 9% between 2 and 3 (rank 3, average: 2.45 +/- 0.12) and 7% between 3 and 4 (rank 4, average: 3.54 +/- 0.10). Glomeruli of the same rats at Ax were ranked according to severity of sclerosis, and then divided into percentile groups, corresponding to the percent of distribution at Bx. The 48% least sclerotic glomeruli at Ax had average SI of 0.69 +/- 0.08, the next 36% 2.58 +/- 0.11, and next 9% 3.97 +/- 0.02 and the most sclerotic 7% 4.00 +/- 0.00. Thus, sclerosis advanced during the last four weeks after biopsy in all glomeruli, with more accelerated progression occurring toward later stages of sclerosis.(ABSTRACT TRUNCATED AT 250 WORDS)

L6 ANSWER 133 OF 166 MEDLINE on STN
ACCESSION NUMBER: 92015889 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1920934
TITLE: Treatment of latent diabetic nephropathy with ACE inhibitor alacepril.
AUTHOR: Hashimoto T
CORPORATE SOURCE: Department of Medicine, Inazawa City Hospital.
SOURCE: Nippon Jinzo Gakkai shi, (1991 Jun) Vol. 33, No. 6, pp. 549-56.
Journal code: 7505731. ISSN: 0385-2385.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199111
ENTRY DATE: Entered STN: 24 Jan 1992
Last Updated on STN: 24 Jan 1992
Entered Medline: 20 Nov 1991

AB Latent diabetic nephropathy with no complication such as retinopaty and hypertension was treated with Alacepril, an ACE inhibitor. This study enrolled 10 patients with microalbuminuria ranging from 5 mg/day (5 mg/gCr) to 50 mg/day (30 mg/gCr). Histological changes due to diabetic nephropathy were confirmed by renal biopsy performed in 4 of 10 patients. All the patients were divided into 2 groups; 5 patients were given 25 mg of Alacepril for 6 months and the remaining 5

patients were employed as the control. As the results, the mean blood pressure was decreased from 92.7 +/- 9.0 mmHg to 87.3 +/- 11.3 mmHg in Alacepril group but these changes were not statistically significant. Microalbuminuria were significantly decreased from 17.33 +/- 7.82 mg/gCr to 10.43 +/- 4.14 mg/gCr during 6 months in the Alacepril group while in the control group, no significant changes were observed in blood pressure and microalbuminuria. Creatinine clearances were not significantly changed in both groups. These findings suggest that Alacepril is useful in improving microalbuminuria of latent diabetic nephropathy.

L6 ANSWER 134 OF 166 MEDLINE on STN
ACCESSION NUMBER: 91347601 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1879096
TITLE: Pharmacokinetics of newer drugs in patients with renal impairment (Part II).
AUTHOR: Singlas E; Fillastre J P
CORPORATE SOURCE: Pharmacie Clinique, Hopital Bicetre, le Kremlin Bicetre, France.
SOURCE: Clinical pharmacokinetics, (1991 May) Vol. 20, No. 5, pp. 389-410. Ref: 127
Journal code: 7606849. ISSN: 0312-5963.
PUB. COUNTRY: New Zealand
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199110
ENTRY DATE: Entered STN: 20 Oct 1991
Last Updated on STN: 20 Oct 1991
Entered Medline: 2 Oct 1991

AB Cardiovascular diseases occur frequently in patients with renal failure. Any pharmacokinetic impairment in these diseases should be considered when individualizing drug therapy. The pharmacokinetics of new cardiovascular drugs in uraemic patients are reviewed: alpha- and beta-blocking agents, ACE inhibitors, centrally acting antihypertensive agents, calcium antagonists, antiarrhythmic agents and inotropic agents. Guidelines are proposed for adjustment of dosage regimens as a function of renal impairment. Renal or extrarenal elimination of drugs and their metabolites, and the activity of the latter, are taken into account. The disposition of new drugs such as flestolol, alacepril, delapril, propafenone, milrinone or enoximone, is not well documented in patients with renal failure. Further characterizations of the elimination of these compounds are needed and the potential therapeutic or toxic effects of the metabolites require evaluation to determine whether the dosage needs to be adjusted. Until such investigations are performed, those drugs should not be used in uraemic patients; if no therapeutic alternative is available, clinical controls are necessary at regular intervals. Relationships between pharmacological or therapeutic effects and drug plasma concentrations should be evaluated for such long term use drugs. The knowledge of a plasma concentration therapeutic window is important to provide information which will be useful in determining appropriate drug dosage in renal failure.

L6 ANSWER 135 OF 166 MEDLINE on STN
ACCESSION NUMBER: 91297882 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2068835
TITLE: Quinapril: a new second-generation ACE inhibitor.
AUTHOR: Cetnarowski-Cropp A B
CORPORATE SOURCE: Cardiology Branch, National Heart, Lung, and Blood Institute, Warren Grant Magneson Clinical Center, Bethesda, MD 20892.

SOURCE: DICP : the annals of pharmacotherapy, (1991 May) Vol. 25, No. 5, pp. 499-504. Ref: 49
Journal code: 8904338. ISSN: 1042-9611.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199108
ENTRY DATE: Entered STN: 1 Sep 1991
Last Updated on STN: 1 Sep 1991
Entered Medline: 13 Aug 1991

AB Quinapril is a new non-sulfhydryl angiotensin-converting enzyme (ACE) inhibitor. The drug undergoes hepatic hydrolysis into its major active diacid metabolite, quinaprilat, and two minor inactive metabolites. On a weight basis quinaprilat is three times as potent an ACE inhibitor as quinapril. Approximately 60 percent of an oral dose of quinapril is absorbed. In contrast with captopril, the absorption of quinapril is unaffected by food. Peak serum concentrations of quinapril and quinaprilat are achieved within one and two hours, respectively. Approximately 61 percent of an orally administered dose is excreted in the urine, principally as quinaprilat. The elimination half-life of quinaprilat is three hours, but is prolonged up to 11 hours in patients with renal dysfunction. Quinapril dose reduction is recommended in patients with a creatinine clearance of 0.50 mL/sec or less. In the elderly the elimination of quinaprilat is reduced and correlates well with renal function. In patients with cirrhosis the hydrolysis of quinapril to quinaprilat is impaired resulting in lower plasma quinaprilat concentrations and up to a two-fold increase in quinapril half-life. Quinaprilat has a strong binding capacity to tissue ACE allowing for once-daily dosing. The recommended starting dose for quinapril is 20 mg/d. The nature and incidence of adverse reactions to quinapril are similar to those of enalapril and captopril. Quinapril's antihypertensive efficacy is equal to that of captopril and enalapril. A small number of patients with congestive heart failure (CHF) have been treated with quinapril. Preliminary data indicate that quinapril is an equally effective therapeutic alternative to presently available ACE inhibitors in the treatment of CHF. (ABSTRACT TRUNCATED AT 250 WORDS)

L6 ANSWER 136 OF 166 MEDLINE on STN
ACCESSION NUMBER: 91276175 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2055428
TITLE: Prevention of albuminuria by captopril in diabetic rats.
AUTHOR: Reddi A S
CORPORATE SOURCE: Department of Medicine, UMDNJ-New Jersey Medical School, Newark 07103.
SOURCE: General pharmacology, (1991) Vol. 22, No. 2, pp. 323-8.
Journal code: 7602417. ISSN: 0306-3623.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199107
ENTRY DATE: Entered STN: 18 Aug 1991
Last Updated on STN: 18 Aug 1991
Entered Medline: 31 Jul 1991

AB 1. Streptozotocin diabetic rats were treated with captopril (50 mg l), an angiotensin converting enzyme-inhibitor, in drinking water for 20 weeks. 2. Systolic blood pressure and 24-hr urinary excretions of heparan sulfate and albumin were done at 2, 8, 16 and 20 weeks. 3. At the end of 20 weeks, all rats were killed, kidneys removed and glomeruli isolated. 4. Total glycosaminoglycan and heparan sulfate synthesis were

determined by incubating glomeruli in the presence of 35S-sulfate. 5. Captopril significantly lowered blood pressure in diabetic rats 8 weeks after treatment. 6. Diabetic glomeruli synthesized less total glycosaminoglycan and heparan sulfate than glomeruli from nondiabetic rats. 7. Further characterization of heparan sulfate by ion-exchange chromatography showed that the fraction eluted with 1 M NaCl was significantly lower and the fraction eluted with 1.25 M NaCl significantly higher in diabetic than in normal rats. 8. Therapy with captopril normalized not only glomerular synthesis and content but also various fractions of heparan sulfate in diabetic rats. 9. Excretions of heparan sulfate and albumin were significantly higher in diabetic than in nondiabetic rats. 10. Captopril therapy did significantly lower but not normalize both these excretions in diabetic rats. 11. The data suggest that catopril therapy improves albuminuria through preservation of glomerular heparan sulfate and prevention of its urinary loss in diabetic rats.

L6 ANSWER 137 OF 166 MEDLINE on STN
ACCESSION NUMBER: 91220824 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1850941
TITLE: Comparison of lisinopril and captopril in the treatment of left ventricular congestive heart failure--influence of duration of action on efficacy and safety.
AUTHOR: Giles T D
CORPORATE SOURCE: Department of Medicine, Tulane University School of Medicine, New Oreleans, Louisiana.
SOURCE: Zeitschrift fur Kardiologie, (1991) Vol. 80 Suppl 2, pp. 35-9. Ref: 15
Journal code: 0360430. ISSN: 0300-5860.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199106
ENTRY DATE: Entered STN: 23 Jun 1991
Last Updated on STN: 23 Jun 1991
Entered Medline: 5 Jun 1991

AB Data from the lisinopril-captopril comparison trial (6), as well as other data (1, 8, 14, 10) indicate that both long- and short-acting ACEI are effective and safe for the treatment of CHF. An improved effect on LV function and signs and symptoms of CHF as a result of more prolonged unloading of the heart by long-acting ACEI is suggested by the lisinopril-captopril comparison trial, but requires confirmation. An effect on renal function is expected with ACEI treatment of CHF, i.e., increase in BUN and serum creatinine; the greater increase in BUN by lisinopril as compared to captopril reflects more the potency and duration of action of the drug rather than a more serious diverse consequence. In patients with renal insufficiency (serum creatinine greater than 1.6 mg/dl), the more potent, longer-acting ACEI may be required. Advanced CHF, i.e. Class III-IV (NYHA), is a clear indication for the use of ACEI, both for improvement in symptoms and mortality. Indication for ACEI treatment of patients with less severe heart failure awaits the results on ongoing clinical trials.

L6 ANSWER 138 OF 166 MEDLINE on STN
ACCESSION NUMBER: 91176894 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2078997
TITLE: Newer ACE inhibitors. A look at the future.
AUTHOR: Salvetti A
CORPORATE SOURCE: Cattedra di Terapia Medica Sistematica, University of Pisa, Italy.
SOURCE: Drugs, (1990 Dec) Vol. 40, No. 6, pp. 800-28. Ref: 205

Journal code: 7600076. ISSN: 0012-6667.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199105
ENTRY DATE: Entered STN: 19 May 1991
Last Updated on STN: 19 May 1991
Entered Medline: 2 May 1991

AB Available information indicates that about 78 new molecules belonging to the class of angiotensin converting enzyme (ACE) inhibitors are under investigation, and that at least 11 or 12 of the newer ACE inhibitors will be available for clinical use. The newer ACE inhibitors can be classified, according to the zinc ion ligand of ACE, into 3 main chemical classes: sulfhydryl-, carboxyl- and phosphoryl-containing ACE inhibitors. All the newer sulfhydryl-containing ACE inhibitors differ from captopril since they are prodrugs, and among them alacepril and probably moveltipril (altiopril, MC 838) are converted in vivo to captopril. When compared with captopril, they show a slower onset and a longer duration of action, and obviously the same route of elimination. Zofenopril, a prodrug that is converted in vivo to the active diacid, shows a greater potency, a similar peak time and a longer duration of action than captopril and, unlike captopril, partial elimination through the liver. The newer carboxyl-containing ACE inhibitors are prodrugs which are converted in vivo to active diacids. Like enalaprilat, they are excreted via the kidney; the exception is spirapril, which is totally eliminated by the liver. Compared to enalapril, benazepril shows an earlier peak time and a slightly shorter terminal half-life, cilazapril and ramipril have an earlier peak time and even longer terminal half-life, perindopril shows similar peak time and terminal half-life, while delapril, quinapril and spirapril show an earlier peak time and a shorter half-life. The phosphoryl-containing ACE inhibitors belong to a new chemical class. Fosinopril is a prodrug which is converted to the active diacid in vivo, shows a relatively late peak time, a long terminal half-life, and is eliminated partially by the liver. SQ 29852, the only newly developed ACE inhibitor which is not a prodrug, seems to be more effective than captopril, with a much longer lasting effect and elimination through the kidney. When the differences in potency between these drugs are compensated by dosage adjustment, all the newer ACE inhibitors are expected to exert a similar amount of inhibition of circulating ACE, and therefore to inhibit to a similar extent the generation of circulating angiotensin II and the breakdown of bradykinin. Obviously they may differ in timing and the duration of circulating ACE inhibition according to their pharmacokinetic properties. With regard to the possibility that they may stimulate prostaglandin synthesis, it is suggested that this action, which does not seem to be specific to this drug class, plays only a minor role in their antihypertensive action; the hypothesis that the sulfhydryl group exerts an additional stimulating action remains to be proved. (ABSTRACT TRUNCATED AT 400 WORDS)

L6 ANSWER 139 OF 166 MEDLINE on STN
ACCESSION NUMBER: 91162915 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2074650
TITLE: Importance of angiogenic action of angiotensin II in the glomerular growth of maturing kidneys.
AUTHOR: Fogo A; Yoshida Y; Yared A; Ichikawa I
CORPORATE SOURCE: Department of Pathology, Vanderbilt University School of Medicine, Nashville, Tennessee.
CONTRACT NUMBER: DK 37868 (NIDDK)
DK 37869 (NIDDK)
DK 42131 (NIDDK)
+
SOURCE: Kidney international, (1990 Dec) Vol. 38, No. 6, pp.

1068-74.
Journal code: 0323470. ISSN: 0085-2538.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199104
ENTRY DATE: Entered STN: 5 May 1991
Last Updated on STN: 5 May 1991
Entered Medline: 18 Apr 1991

AB We studied the effect of three antihypertensive drugs on the growth of glomeruli in four- to five-week-old Munich-Wistar rats (N = 24), which were undergoing rapid maturation processes. Young rats were given an angiotensin converting enzyme inhibitor (ACEI, enalapril , 50 mg/liter drinking water), verapamil (50 mg/liter) or hydralazine (80 mg/liter) or no treatment for six weeks. Body weight increased comparably in the treatment groups and age-matched controls, reaching on average 197 +/- 11, 214 +/- 12 and 198 +/- 3 g in ACEI-, verapamil- and hydralazine-treated rats, respectively, versus 218 +/- 6 g in control rats. Glomerular hemodynamic patterns, including glomerular capillary pressure, measured in maturing rats after one and six weeks of ACEI treatment were unaffected by ACEI. Mean planar area of glomeruli (PAmean) achieved was smaller than control in ACEI rats (6.60 +/- 0.20 x 10(-3) mm2 vs. 5.37 +/- 0.22, respectively, P less than 0.005), but not in rats treated with other antihypertensive drugs. Furthermore, the maturational PAmean increase in rats given ACEI for six weeks was, on average, only half of that achieved by age-matched controls not given ACEI, in contrast to normal maturational growth with hydralazine or verapamil (29% increase in PAmean from normal baseline in ACEI vs. 52%, 53% and 59% increases in verapamil, hydralazine and control, respectively). In contrast, comparable PAmean values were found in adults with (7.08 +/- 0.22 x 10(-3)mm2, N = 6) and without (6.98 +/- 0.33 x 10(-3)mm2, N = 6) ACEI treatment given for six weeks. Therefore, ACEI, but not verapamil and hydralazine, causes growth retardation in maturing glomeruli.(ABSTRACT TRUNCATED AT 250 WORDS)

L6 ANSWER 140 OF 166 MEDLINE on STN
ACCESSION NUMBER: 91107827 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2273086
TITLE: Pharmacokinetics of quinapril and its active metabolite quinaprilat during continuous ambulatory peritoneal dialysis.
AUTHOR: Swartz R D; Starmann B; Horvath A M; Olson S C; Posvar E L
CORPORATE SOURCE: Department of Internal Medicine, University of Michigan Medical Center, Ann Arbor 48109-0364.
SOURCE: Journal of clinical pharmacology, (1990 Dec) Vol. 30, No. 12, pp. 1136-41.
Journal code: 0366372. ISSN: 0091-2700.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199102
ENTRY DATE: Entered STN: 29 Mar 1991
Last Updated on STN: 29 Mar 1991
Entered Medline: 22 Feb 1991

AB The pharmacokinetics of quinapril, a novel angiotensin converting enzyme (ACE) inhibitor, and its active metabolite, quinaprilat, were determined following a single 20-mg oral dose of quinapril in six patients with chronic renal failure maintained on continuous ambulatory peritoneal dialysis (CAPD). Overall, quinapril was well tolerated by these CAPD patients, with mild and transient side effects, not unexpected in this clinical setting, which included pruritus, headache, nausea, and

cough. Blood pressure reduction was observed in four of six patients, with onset reliably two to four hours after dosing and duration up to 48 hours, associated with quinaprilat concentrations in plasma above 90 ng/mL for at least 33 hours postdose. Two patients experienced significant hypotension, systolic blood pressure below 90 mm Hg, which responded promptly to oral fluid administration and/or reduction in dialysate tonicity. The pharmacokinetic profile of quinapril in these CAPD patients was not significantly different from that previously observed in healthy subjects with normal renal function and in patients with moderate to severe renal dysfunction not yet requiring dialysis (RDND). The apparent elimination half-life of quinapril was approximately one hour, with negligible dialysate excretion. The pharmacokinetic profile of quinaprilat in these CAPD patients was similar to that previously observed in patients with RDND. The elimination half-life of quinaprilat was markedly prolonged when compared to that in healthy subjects and averaged 20 hours, with only a small amount of quinaprilat excreted in dialysate (mean = 2.6% of total dose).(ABSTRACT TRUNCATED AT 250 WORDS)

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L6 ANSWER 120 OF 166 MEDLINE on STN
ACCESSION NUMBER: 93058322 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1432566
TITLE: Hypotensive effect of a phosphorus-containing novel angiotensin converting enzyme inhibitor, (S)-1-[6-amino-2[[hydroxy(4-phenylbutyl)phosphinyl]oxy]-1-oxohexyl]-L-proline (SQ 29,852) in conscious hypertensive dogs.
AUTHOR: Ohara N; Takizawa M; Yokota S; Ogawa N; Katsumura H; Ono H
CORPORATE SOURCE: Department of Pharmacology and Toxicology, Food and Drug Safety, Kanagawa, Japan.
SOURCE: Journal of pharmacobio-dynamics, (1992 Jun) Vol. 15, No. 6, pp. 267-76.
Journal code: 7901854. ISSN: 0386-846X.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199212
ENTRY DATE: Entered STN: 22 Jan 1993
Last Updated on STN: 22 Jan 1993
Entered Medline: 3 Dec 1992
AB The hypotensive efficacy of (S)-1-[6-amino-2[[hydroxy(4-phenylbutyl) phosphinyl]oxy]-1-oxohexyl]-L-proline (SQ 29,852), a phosphorus-containing novel angiotensin converting enzyme inhibitor (ACEI) was examined in conscious two-kidney, one-clip Goldblatt hypertensive dogs. The acute hypotensive effect of SQ 29 852 was compared with that of captopril or enalapril at 3 mg/kg, p.o., for each, and the potencies were ranked as follows, enalapril greater than SQ 29,852 greater than captopril. On the other hand, the hypotension caused by repetitive dosing with SQ 29,852 (3 mg/kg, p.o./d for 7 d followed by another 7-d treatment with 10 mg/kg, p.o./d) was somewhat more marked than that by enalapril at the same dosage. Blood urea nitrogen (BUN) increased in all the animals given enalapril, while that in all of the SQ 29,852-treated animals did not increase. These results indicate that SQ 29,852 is a potent, and long-lasting ACEI with a possible low incidence of side effects.

L6 ANSWER 121 OF 166 MEDLINE on STN
ACCESSION NUMBER: 93022328 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1405318
TITLE: Renal effect of anti-hypertensive drugs depends

on sodium diet in the excision remnant kidney model.
AUTHOR: Terzi F; Beaufils H; Laouari D; Burtin M; Kleinknecht C
CORPORATE SOURCE: INSERM U. 192, Hopital Necker Enfants-Malades, Paris, France.
SOURCE: Kidney international, (1992 Aug) Vol. 42, No. 2, pp. 354-63.
Journal code: 0323470. ISSN: 0085-2538.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199211
ENTRY DATE: Entered STN: 22 Jan 1993
Last Updated on STN: 22 Jan 1993
Entered Medline: 13 Nov 1992

AB Angiotensin converting enzyme inhibitors (ACEI) are believed to protect remnant kidney, but all previous studies used the ligation model which causes severe hypertension, and very few have compared drugs in rats having similar control of blood pressure (BP). We compared rats with uremia obtained by 70% excision of total renal mass, a model which causes mild, late hypertension. Study I compared the effects of enalapril (E), cicletanine (C) and placebo (P) in uremic (U) rats fed a 0.50% (normal-high) Na diet. Study II compared the effects of E, C, P, and guanfacine (G) in U rats fed a diet restricted to 0.25% Na (normal-low). In study I, UP rats developed progressive hypertension (140, 146, 160 and 166 mm Hg at 3, 6, 9 and 12 weeks), proteinuria (240 mg/day at 9 and 12 weeks) which were not affected by E or C. The occurrence of end-stage renal disease (ESRD) led to the sacrifice of all rats after three months. All three groups had similar severe renal lesions (over 25% sclerosed glomeruli in 5 of 10 UP, 9 of 14 UE, 7 of 14 UC rats, with huge cystic tubular dilatations). In study II, rats could be sacrificed later (6 months) and had evidence of less severe renal disease. All the drugs tested prevented hypertension throughout the study (P less than 0.001), with lowest values in UE rats. E and G, but not C, reduced proteinuria. Renal damage was reduced with E and G, but not with C, despite similar BP in C and G rats. Thus, in contrast with what was obtained in the ligation model, ACEI affected neither the BP nor the renal lesions of rats made uremic by renal excision and fed a 0.50% Na diet. Moderate Na restriction improved the consequences of nephron loss and restored the anti-hypertensive effect of drugs. However, these drugs had a different effect on renal preservation: it was dramatic with E, good with G, and undetectable with C.

L6 ANSWER 122 OF 166 MEDLINE on STN
ACCESSION NUMBER: 92363061 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1499863
TITLE: Diminished glomerular capillary hydraulic conductivity precedes morphologic changes in experimental diabetes mellitus in the rat.
AUTHOR: Ellis E N; Wiegmann T B; Savin V J
CORPORATE SOURCE: Department of Pediatrics, University of Arkansas for Medical Sciences, Little Rock.
CONTRACT NUMBER: 22040
SOURCE: Diabetes, (1992 Sep) Vol. 41, No. 9, pp. 1106-12.
Journal code: 0372763. ISSN: 0012-1797.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199209
ENTRY DATE: Entered STN: 25 Sep 1992
Last Updated on STN: 25 Sep 1992

Entered Medline: 17 Sep 1992

AB Glomerular ultrafiltration coefficient, Kf, is diminished in established diabetic nephropathy. To determine whether Kf is decreased because of a decrease in capillary area, A, and or in hydraulic conductivity, Lp, glomerular Kf and morphometric parameters were measured, and Lp was calculated in glomeruli of young rats with STZ-induced DM and in control rats. STZ was administered to Fischer 344 rats that weighted 50-75 g; glomeruli were examined after 3 or 5 mo of DM, and their structure and function was compared with that of control rats. The effects of insulin or of an ACEI, enalapril, also were assessed after 3 or 5 mo. Growth of DM rats was markedly impaired, and their ratio of kidney weight to body weight was increased. Ccr was proportional to rat weight, and the ratio of Ccr to body weight was not different in DM and control rats. At 3 mo, average volume of glomeruli isolated from DM rats was less than that of glomeruli from control rats. In contrast, glomerular volume after 5 mo was equal in DM and control rats. No increase in GBM thickness or mesangial volume was observed, nor was any decrease seen in GBM area in DM rats at 5 mo. Kf was lower in DM rats than controls after 3 mo, but not after 5 mo. The Lp of DM and control glomeruli did not differ at 3 mo, but was lower in DM at 5 mo. Insulin therapy improved somatic growth and increased kidney and glomerular size in DM rats; the kidney weight/body weight ratio remained elevated. (ABSTRACT TRUNCATED AT 250 WORDS)

L6 ANSWER 123 OF 166 MEDLINE on STN

ACCESSION NUMBER: 92341704 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1635354
TITLE: Blood pressure-independent effect of angiotensin inhibition on vascular lesions of chronic renal failure.
AUTHOR: Kakinuma Y; Kawamura T; Bills T; Yoshioka T; Ichikawa I; Fogo A
CORPORATE SOURCE: Department of Pediatrics, Vanderbilt University Medical Center, Nashville, Tennessee.
CONTRACT NUMBER: DK-37868 (NIDDK)
DK-40527 (NIDDK)
DK-42131 (NIDDK)
+
SOURCE: Kidney international, (1992 Jul) Vol. 42, No. 1, pp. 46-55. Journal code: 0323470. ISSN: 0085-2538.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199208
ENTRY DATE: Entered STN: 11 Sep 1992
Last Updated on STN: 11 Sep 1992
Entered Medline: 26 Aug 1992

AB Previous studies in experimental models of progressive renal failure have shown that the capacity of antihypertensive drugs to protect glomeruli from sclerosis is often unpredictable from their effect on systemic blood pressure. The present study was undertaken to ascertain whether this systemic blood pressure-independent structure-preserving effect of antihypertensives, particularly angiotensin II converting enzyme inhibitors (ACEI), is confined to the glomerulus or not, as well as whether this effect is mediated via angiotensin II (Ang II). The following experimental drug regimens were used in the rat model of subtotal nephrectomy (sNPX): so-called triple therapy [TRX; a combination of reserpine 5 mg/liter drinking water (DW), hydralazine 80 mg/liter DW and hydrochlorothiazide 25 mg/liter DW], or ACEI (either captopril, CPL, 600 mg/liter DW, enalapril, ENL, 400 mg/liter DW or lisinopril, LSL, 200 mg/liter DW), or a novel Ang II receptor antagonist (Ang IIR, L-158,809, 20 mg/liter DW). These dosages were identified in pilot studies to be the minimum required to control systemic blood pressure in the early phase up to 12 weeks. In addition, a separate

group was treated with a higher dose of L-158,809 (80 mg/liter DW) with equipotent systemic pressor effect. Treatment was initiated eight weeks after subtotal nephrectomy following renal biopsy, and animals were sacrificed at 16 weeks. In ACEI treated rats, carotid arterial wall thickening (WT), defined as ratio of media thickening to radius of outer vessel wall, was similar to normal age-matched control (0.073 in all ACEI treated rats, vs. 0.074 in normal control) and significantly less than with TRX (ratio 0.118) or untreated sNPX (0.130). Even more remarkably, coronary arteriole WT in ACEI -treated rats averaged 0.139, a value less than one half and one third of TRX (0.298) and untreated sNPX control (0.388), respectively. Similar results were obtained for mesenteric artery WT. These findings were closely paralleled by changes of glomerular sclerosis. In untreated sNPX control rats, glomerular sclerosis increased from biopsy to autopsy specimens by an average of 458%. Although TRX dampened the degree of increase in sclerosis to on average 212%, this protective effect was far less than that achieved by ACEI. In the latter, sclerosis increased on average only 65% from biopsy to autopsy. Although all ACEIs were more effective than TRX, captopril and lisinopril groups showed greatest benefit at these doses. Ang IIR also protected renal and extrarenal structures with 34% increase of sclerosis index in low dose and WT 0.088, 0.117 and 0.112, respectively in carotid, mesenteric and coronary arteries.(ABSTRACT TRUNCATED AT 400 WORDS)

L6 ANSWER 124 OF 166 MEDLINE on STN
ACCESSION NUMBER: 92246105 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1575171
TITLE: Does blood pressure reduction necessarily compromise cardiac function or renal hemodynamics? Effects of the angiotensin-converting enzyme inhibitor quinapril.
AUTHOR: Kjeldsen S E; Gupta R K; Krause L; Weder A B; Julius S
CORPORATE SOURCE: Department of Internal Medicine, Ullevaal University Hospital, Oslo, Norway.
SOURCE: American heart journal, (1992 May) Vol. 123, No. 5, pp. 1433-8.
Journal code: 0370465. ISSN: 0002-8703.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199206
ENTRY DATE: Entered STN: 19 Jun 1992
Last Updated on STN: 19 Jun 1992
Entered Medline: 3 Jun 1992

AB Clinical studies indicate that the angiotensin-converting enzyme inhibitor quinapril is an effective antihypertensive agent when administered once daily. At the end of a 4-week, double-blind crossover trial comparing quinapril and placebo, patients were admitted for a hemodynamic profile study 12 hours after taking the previous dose. A final 20 mg dose of quinapril had no additional effect on blood pressure. This is interesting inasmuch as the plasma half-life of the active metabolite quinaprilat is approximately 2 hours and the effective accumulation half-life is approximately 3 hours. The blood pressure reduction in patients with mild hypertension receiving long-term quinapril therapy may be more closely related to prolonged angiotensin-converting enzyme inhibition or to an effect on tissue angiotensin II concentration than to the plasma half-life. This may be the case particularly for cardiac output and renal circulation, because quinapril lowers total vascular resistance without increasing cardiac output or disturbing autoregulation of renal blood flow. Reduced ventricular wall stress, improved diastolic function, and lower renal perfusion pressure may spare cardiac function and glomeruli from hypertensive

vascular damage.

L6 ANSWER 125 OF 166 MEDLINE on STN
ACCESSION NUMBER: 92235335 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1569237
TITLE: The pharmacokinetics of quinapril and its active metabolite, quinaprilat, in patients with various degrees of renal function.
AUTHOR: Halstenson C E; Opsahl J A; Rachael K; Olson S C; Horvath A M; Abraham P A; Posvar E L
CORPORATE SOURCE: Division of Nephrology, Hennepin County, Medical Center, Minneapolis, MN 55415.
SOURCE: Journal of clinical pharmacology, (1992 Apr) Vol. 32, No. 4, pp. 344-50.
Journal code: 0366372. ISSN: 0091-2700.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199205
ENTRY DATE: Entered STN: 12 Jun 1992
Last Updated on STN: 12 Jun 1992
Entered Medline: 27 May 1992

AB Single- and multiple-dose pharmacokinetics of quinapril and its active metabolite, quinaprilat, were determined after oral administration of 20 mg quinapril HCl on day 1 and days 4 through 10 in 17 normotensive subjects with various degrees of renal function. Blood and urine samples were collected over 72- and 24-hour periods, respectively, after the first single dose and last multiple dose for measurement of quinapril and quinaprilat concentrations. The renal clearance of quinapril and quinaprilat decreased with increasing renal insufficiency but did not result in significant changes in quinapril pharmacokinetics in patients with renal impairment. In contrast, quinaprilat maximum plasma concentration, trough and peak steady-state plasma concentrations, area under the plasma concentration-time curve, and half-life increased significantly with increasing renal insufficiency. The disposition of quinapril and quinaprilat was unchanged from single to multiple doses. Small changes in the pharmacokinetic disposition of quinapril, together with a decreased rate of quinaprilat elimination, resulted in increased quinaprilat plasma concentrations following administration of both single and multiple quinapril doses to normotensive patients with renal impairment. Thus, quinapril dosage adjustment may be required in some patients with renal impairment.

L6 ANSWER 126 OF 166 MEDLINE on STN
ACCESSION NUMBER: 92227295 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1808367
TITLE: Effect of angiotensin converting enzyme inhibitor and calcium channel blocker on renal function of spontaneously hypertensive rat.
AUTHOR: Endo M
CORPORATE SOURCE: Department of Medicine, Kidney Center, Tokyo Women's Medical College.
SOURCE: Nippon Jinzo Gakkai shi, (1991 Nov) Vol. 33, No. 11, pp. 1161-72.
Journal code: 7505731. ISSN: 0385-2385.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199205
ENTRY DATE: Entered STN: 7 Jun 1992

Last Updated on STN: 7 Jun 1992
Entered Medline: 18 May 1992

AB Effect of angiotensin converting enzyme inhibitor (ACEI) and calcium channel blockers (CaB) on renal blood flow (RBF), glomerular filtration rate (GFR), and autoregulation (AR) of RBF were studied on the uninephrectomized spontaneously hypertensive rat (SHR) under the conditions of high (H) and low (L) salt loading. SHR was given with 0.9% or 0.09% NaCl solution as drinking water (GH, GL). Each group was divided into three groups for treatment with enalapril (Enp) and nitredipine (Nit); i.e. Enp group (GHE, GLE), Nit group (GHN, GLN) and control group (GHC, GLC). After 6 weeks, inulin clearance (Cin) was determined and RBF was measured by means of an electromagnetic flow meter. The renal arterial pressure was lowered by clamping and changes in RBF and AR were examined. Cin showed higher values of 1.85 and 1.69 ml/min in GHN and GLN, as compared to be 1.33 and 1.28 ml/min in GHC and GLC (p less than 0.01). Filtration fraction (FF) showed lower values of 0.18 and 0.20 ml/min in GHE and GLE (p less than 0.01), whereas 0.29 and 0.30 in GHC and GLC respectively. RBF was markedly lower at 7.4 ml/min in GLC as compared to 9.9 ml/min in GHC (p less than 0.01). In GH, GHE showed a higher value of 11.6 ml/min, as compared to GHC (p less than 0.01). In GL, comparing with GLC the value was much higher of 12.1 ml/min in GLE (p less than 0.01). AR of RBF diminished in GLC at higher blood pressure as compared to GHC (p less than 0.01). It was maintained at lower blood pressure in GLE (p less than 0.01), but there were no significant differences between four groups; i.e. GLN, GHC, GHE and GHN. In summary, low salt loading reduced RBF and suppressed AR. Enp elevated RBF, lowered FF and caused AR to be maintained even at lower blood pressure. Nit elevated RBF and GFR without changing FF, and did not suppress AR. These results indicate that, in hypertension complicated with moderate dysfunction, both ACEI and CAB are expected to exhibit the beneficial effects on maintenance of renal circulation, despite though the different mechanism.

L6 ANSWER 127 OF 166 MEDLINE on STN
ACCESSION NUMBER: 92188923 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1546641
TITLE: Comparative pharmacokinetics of captopril, enalapril, and quinapril.
AUTHOR: Vertes V; Haynie R
CORPORATE SOURCE: Case Western Reserve University, Mt. Sinai Medical Center, Cleveland, Ohio 44106.
SOURCE: The American journal of cardiology, (1992 Apr 2) Vol. 69, No. 10, pp. 8C-16C. Ref: 45
Journal code: 0207277. ISSN: 0002-9149.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199204
ENTRY DATE: Entered STN: 24 Apr 1992
Last Updated on STN: 24 Apr 1992
Entered Medline: 15 Apr 1992

AB This review compares the metabolism and pharmacokinetic profiles of captopril, the first orally active angiotensin-converting enzyme (ACE) inhibitor, and 2 newer ACE inhibitors, enalapril and quinapril. Captopril differs from both enalapril and quinapril in that its chemical structure contains a sulfhydryl group, the presence of which may be important in the development of adverse reactions. Captopril also differs from enalapril and quinapril in its ability to be metabolized in plasma. Enalapril and quinapril are both de-esterified, most likely in the liver, to their active metabolites, enalaprilat and quinaprilat. All 3 ACE inhibitors are eliminated primarily via renal excretion, and renal dysfunction markedly increases the area under the time

versus plasma concentration curves. Hepatic dysfunction also slows the conversion of enalapril and quinapril to their active metabolites. There is evidence that both captopril and enalapril, but not quinapril, may accumulate with repeated dosing. The pharmacokinetics of these agents are not significantly modified by co-administration of other drugs. However, captopril does cause marked increases in trough plasma levels of digoxin. Overall, the pharmacokinetic profiles of captopril, enalapril, and quinapril make them suitable for a wide range of patients with hypertension or congestive heart failure.

L6 ANSWER 128 OF 166 MEDLINE on STN
ACCESSION NUMBER: 92188920 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1546639
TITLE: Adverse effects of angiotensin-converting enzyme inhibitors in antihypertensive therapy with focus on quinapril.
AUTHOR: Materson B J
CORPORATE SOURCE: Department of Medicine, University of Miami, Florida.
SOURCE: The American journal of cardiology, (1992 Apr 2) Vol. 69, No. 10, pp. 46C-53C. Ref: 54
Journal code: 0207277. ISSN: 0002-9149.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199204
ENTRY DATE: Entered STN: 24 Apr 1992
Last Updated on STN: 24 Apr 1992
Entered Medline: 15 Apr 1992

AB Angiotensin-converting enzyme (ACE) inhibitors are useful first-line drugs in the therapy of mild and moderate hypertension. Adverse reactions to this drug class are rarely serious. Hypotension, cough, rash, and taste disturbance are uncommon; reduced glomerular filtration and hyperkalemia occur infrequently; angioedema is rare and neutropenia is extremely rare. Quinapril is a new ACE inhibitor that is converted to biologically active quinaprilat in the liver. This ACE inhibitor has a rapid onset of action and inhibits local tissue converting enzyme systems in kidney, heart, and brain, as well as in the circulating renin-angiotensin system. Clinically significant adverse effects of quinapril occur at low rates. In 1,771 patients receiving quinapril, the reported incidence of the first occurrence of orthostatic hypotension was comparable to that seen in patients receiving placebo. In other studies, headache was reported by up to 4.7% of patients receiving quinapril, which is comparable to reported incidences of headache in patients receiving other ACE inhibitors. Other adverse events reported at rates greater than 1% include cough with associated rhinitis and bronchitis, dizziness, and somnolence. Such adverse events have only rarely led to the withdrawal of patients from clinical studies of quinapril.

L6 ANSWER 129 OF 166 MEDLINE on STN
ACCESSION NUMBER: 92137555 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1778358
TITLE: Fertility and perinatal/postnatal studies in rats with the angiotensin-converting enzyme inhibitor, quinapril.
AUTHOR: Dostal L A; Kim S N; Schardein J L; Anderson J A
CORPORATE SOURCE: Parke-Davis Pharmaceutical Research Division, Warner-Lambert Company, Ann Arbor, Michigan 48105.
SOURCE: Fundamental and applied toxicology : official journal of the Society of Toxicology, (1991 Nov) Vol. 17, No. 4, pp. 684-95.
Journal code: 8200838. ISSN: 0272-0590.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 199203
ENTRY DATE: Entered STN: 29 Mar 1992
Last Updated on STN: 29 Mar 1992
Entered Medline: 6 Mar 1992

AB Quinapril, an inhibitor of angiotensin-converting enzyme (ACE) and an antihypertensive agent, was evaluated in rats for effects on fertility, reproduction, and perinatal and postnatal development. In a fertility study, male rats were treated by gavage for 60 days prior to and during mating and female rats were treated by gavage for 14 days prior to mating, during mating and gestation, and during lactation with doses of 0, 10, 50, or 100 mg quinapril/kg body weight There were no significant effects on body weight, food consumption, fertility indices, fetal development, or neonatal growth, survival, development, behavior, or reproduction. In a perinatal/postnatal study, administration of quinapril to females at doses of 25, 75, or 150 mg/kg during late gestation and lactation had no effects on parturition, lactation, or postnatal development, but a significant decrease in neonatal body weight during the suckling period was observed at all doses. In a subsequent study, female rats were given 150 mg/kg during late gestation, lactation, or late gestation and lactation. No adverse effects were seen in the dams or the offspring, and no reduction in neonatal body weight was observed. Kidneys from pups whose mothers received quinapril during gestation and/or lactation had minimal juxtaglomerular cell hypertrophy, characteristic of treatment with ACE inhibitors. Low levels of quinaprilat (the major and pharmacologically active metabolite of quinapril) were detected in fetal blood and in neonatal blood, indicating offspring exposure to quinapril. Milk quinaprilat concentrations were 3-5% of the plasma concentrations 3-5 hr after dosing. These studies demonstrate no adverse effects of quinapril on fertility, reproduction, or perinatal and postnatal development.

=> dis his

(FILE 'HOME' ENTERED AT 13:42:16 ON 05 SEP 2006)

FILE 'MEDLINE' ENTERED AT 13:42:36 ON 05 SEP 2006
L1 8297 S TU OP OR BMP OR OSTEOGENIC(W)PROTEIN OR BONE(W)MORPHOGENIC(W)
L2 1296 S L1 AND ACE(W)INHIBITOR OR ACEI
L3 508446 S L2 AND RENAL OR KIDNEY
L4 535 S L2 AND (RENAL OR KIDNEY)
L5 493 S L2 AND ENALAPRIL OR CATOPRIL OR FONSINOPRIL OR TRANDOLOPRIL O
L6 166 S L5 AND (RENAL OR KIDNEY)
L7 166 DUP REM L6 (0 DUPLICATES REMOVED)

=> dis ibib abs l6 110-119

L6 ANSWER 110 OF 166 MEDLINE on STN
ACCESSION NUMBER: 95054610 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7965274
TITLE: Effects of renin-angiotensin system in mediating endothelin-induced renal vasoconstriction: therapeutic implications.
AUTHOR: Chan D P; Clavell A; Keiser J; Burnett J C Jr
CORPORATE SOURCE: Cardiorenal Research Laboratory, Mayo Clinic, Rochester, MN.
CONTRACT NUMBER: HL36634 (NHLBI)
SOURCE: Journal of hypertension. Supplement : official journal of the International Society of Hypertension, (1994 Jul) Vol. 12, No. 4, pp. S43-9.
Journal code: 8501422. ISSN: 0952-1178.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199412
ENTRY DATE: Entered STN: 10 Jan 1995
Last Updated on STN: 10 Jan 1995
Entered Medline: 29 Dec 1994

AB PURPOSE: Experiments were designed to determine whether angiotensin converting enzyme inhibition with quinaprilat can prevent endothelin-mediated decreases in renal blood flow and the glomerular filtration rate in the anesthetized dog. METHODS: To mimic the activation of the renal endothelin system that occurs in a number of cardiorenal disease states, endothelin was administered intrarenally in a group of mongrel dogs. Quinaprilat, the major active metabolite of quinapril, was infused in a separate group. One kidney (group 1) or both kidneys (group 2) were exposed in order to measure renal blood flow by an electromagnetic flow probe. Mean arterial blood pressure was measured through a catheter in a femoral vein. Blood samples were taken to determine plasma renin activity. Urine was collected. RESULTS: The infusion of endothelin decreased renal blood flow and the glomerular filtration rate and increased renal vascular resistance. These renal vascular responses were associated with increased plasma renin activity, indicating activation of the renal renin-angiotensin system. Quinaprilat attenuated the renal vascular responses. CONCLUSIONS: These studies provide further evidence of the importance of the renal renin-angiotensin system in mediating the renal vasoconstrictor actions of endothelin and indicate the therapeutic potential for quinapril in opposing the actions of endothelin in states of excessive endothelin activation.

L6 ANSWER 111 OF 166 MEDLINE on STN
ACCESSION NUMBER: 94349352 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8069900
TITLE: [The effect of a low-protein diet and certain pharmaceutical agents on the course of ablation nephropathy in rats].
Vliv diety o nizkem obsahu bilkovin a nekterych farmak na prubeh ablacni nefropatie u krys.
AUTHOR: Heller J; Cervenka L; Hellerova S
CORPORATE SOURCE: Pracoviste experimentalni mediciny Institutu klinicke a experimentalni mediciny, Praha.
SOURCE: Casopis lekar u c eskych, (1994 Jul 18) Vol. 133, No. 14, pp. 429-33.
Journal code: 0004743. ISSN: 0008-7335.
PUB. COUNTRY: Czech Republic
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Czech
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199409
ENTRY DATE: Entered STN: 6 Oct 1994
Last Updated on STN: 6 Oct 1994
Entered Medline: 27 Sep 1994

AB BACKGROUND. The beneficial effect of a low-protein diet on the course of renal failure after ablation nephropathy in the rat is known; also calcium channel antagonists (CaA) and angiotensin I converting enzyme inhibitors (ACEI) have a protective effect. Because even simple energy restriction retards the development of spontaneous or ablation-induced glomerulosclerosis the authors decided to replace the lacking dietary protein in the low protein diet by starch (disaccharide) and by fat (cereal oil) and compare these two low-protein diets as to their effect on the development of chronic renal failure (CRI) caused by surgical removal of 5/6 of renal parenchyma (5/6 NX). METHODS AND RESULTS. In Wistar rats just after weaning, 5/6 of renal parenchyma were removed surgically. Thereafter, the rats

were fed either a "high-protein" (21%) or two types of a "low-protein" (6%) diet, in one of the latter, the lack of protein was substituted by saccharide, in the other by fat making the substitution "isocaloric" in either case. In all three diet groups, subgroups drinking either tap water or water containing either the ACE-inhibitor enalapril (ena) or the calcium antagonist diltiazem (dil) or both (ena+dil) were formed. On the high-protein diet, an increase in the weight of kidney remnants, in proteinuria and in systolic blood pressure (SBP) was seen. This was prevented by feeding either type of the low-protein diet but also by ena and ena+dilute Ena and ena+dil not only prevented the increase in SBP but actually lowered it significantly. Dil alone also had a SBP-lowering action but offered no protection from kidney hypertrophy and it significantly. Dil alone also had a SBP-lowering action but offered no protection from kidney hypertrophy and proteinuria. No additive protective action of ena+dil or ena+low-protein or ena+dil+low-protein was seen suggesting that the lower limit of these protective actions was reached by the low-protein diet alone. There was no substantial difference between either type of low-protein diet except a small and transient decrease in body weight in the first week on a fat-rich diet. CONCLUSIONS. In the described experiments and with the set-up used the low-protein diet had no effect on the plasma creatinine and urea levels nor on creatinine clearance. The weight of the kidney remnants and proteinuria were significantly higher in animals on a high-protein diet who drank water or water with diltiazem. These changes were suppressed by administration of angiotensin converting enzyme inhibitors either alone or combined with diltiazem. A low- protein diet (both types tested) as well as angiotensin converting enzyme inhibitors improve the course of chronic renal failure in ablation nephropathy in the rat; the authors did not prove an additive effect of the combination of this diet with angiotensin converting enzyme inhibitors.

L6 ANSWER 112 OF 166 MEDLINE on STN
ACCESSION NUMBER: 94336974 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8059025
TITLE: Acute tubular necrosis in kidney transplant patients treated with enalapril.
AUTHOR: Garcia T M; da Costa J A; Costa R S; Ferraz A S
CORPORATE SOURCE: Renal Transplant Unit, Faculty of Medicine of Ribeirao Preto, University of Sao Paulo, Ribeirao Preto, Brazil.
SOURCE: Renal failure, (1994) Vol. 16, No. 3, pp. 419-23. Journal code: 8701128. ISSN: 0886-022X.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CASE REPORTS) Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199409
ENTRY DATE: Entered STN: 20 Sep 1994
Last Updated on STN: 20 Sep 1994
Entered Medline: 15 Sep 1994

AB We report two cases of acute renal failure in renal transplant patients using cyclosporine-A (CsA) after the introduction of angiotensin-converting enzyme inhibitor (ACEI) to control arterial hypertension. They had no renal artery stenosis or acute rejection. Both patients presented severe acute tubular necrosis (ATN), which subsided after discontinuation of the ACEI. Synergistic toxic effect of ACEI and CsA on the renal tubules might explain ATN in these two cases.

L6 ANSWER 113 OF 166 MEDLINE on STN
ACCESSION NUMBER: 94257400 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8198942
TITLE: The pharmacokinetics of quinapril and quinaprilat

in patients with congestive heart failure.
AUTHOR: Begg E J; Robson R A; Ikram H; Richards A M; Bammert-Adams J A; Olson S C; Posvar E L; Reece P A; Sedman A J
CORPORATE SOURCE: Department of Clinical Pharmacology, Christchurch School of Medicine, New Zealand.
SOURCE: British journal of clinical pharmacology, (1994 Mar) Vol. 37, No. 3, pp. 302-4.
Journal code: 7503323. ISSN: 0306-5251.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199407
ENTRY DATE: Entered STN: 14 Jul 1994
Last Updated on STN: 14 Jul 1994
Entered Medline: 7 Jul 1994

AB The pharmacokinetics of quinapril and its active metabolite quinaprilat were studied in 12 patients with congestive heart failure (CHF) after multiple oral doses of 10 mg quinapril twice daily. Six patients had an ejection fraction of < 35% and six had an ejection fraction between 35%-50%. Increases in the apparent elimination half-life and in AUC(0, 12h) values of quinaprilat were associated with smaller ejection fractions, decreased creatinine clearance, and increased patient age. Comparison with data from age-matched controls having comparable renal function suggests that creatinine clearance is the major determinant of quinaprilat clearance. CHF per se appears to have minimal effect. Dosing of quinapril in patients with CHF should be based on their renal function.

L6 ANSWER 114 OF 166 MEDLINE on STN
ACCESSION NUMBER: 94229126 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8174603
TITLE: Structural constraints of inhibitors for binding at two active sites on somatic angiotensin converting enzyme.
AUTHOR: Perich R B; Jackson B; Johnston C I
CORPORATE SOURCE: University of Melbourne, Department of Medicine, Austin Hospital, Heidelberg, Victoria, Australia.
SOURCE: European journal of pharmacology, (1994 Feb 15) Vol. 266, No. 3, pp. 201-11.
Journal code: 1254354. ISSN: 0014-2999.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199406
ENTRY DATE: Entered STN: 20 Jun 1994
Last Updated on STN: 20 Jun 1994
Entered Medline: 3 Jun 1994

AB Angiotensin converting enzyme active sites from rat plasma, lung, kidney and testis were assessed by comparative radioligand binding studies under physiological chloride conditions. Displacement of [125I]Ro 31-8472 from somatic and plasma angiotensin converting enzyme by angiotensin converting enzyme inhibitors of different structure indicated two binding sites (perindoprilat: high affinity carboxyl site, KDC 18 +/- 6 pM), and a single high affinity binding site on testis angiotensin converting enzyme (KDC 20 +/- 1 pM). Displacement of [125I]351A from plasma, somatic and testis angiotensin converting enzyme occurred at a single high affinity binding site. Reduction in affinity at the amino binding site of somatic angiotensin converting enzyme was related to an increased side chain size (lung KDA (pM): Ro 31-8472 175 +/- 38, lisinopril 2205 +/- 1832, and 351A 2271 +/- 489), or hydrophobicity of the competing unlabelled angiotensin converting enzyme inhibitor (lung KDA (pM): quinaprilat 1267 +/- 629 and perindoprilat 824 +/- 6). This trend was reversed at the carboxyl binding site of plasma, somatic

and testis angiotensin converting enzyme. Bradykinin hydrolysis by lung angiotensin converting enzyme was inhibited in a similar manner by cilazaprilat or quinaprilat (F = 0.64, F-test based on the extra sum-of-squares principle; P > 0.05), indicating the angiotensin converting enzyme carboxyl active site predominates in bradykinin cleavage. The data demonstrate that the two binding sites on native plasma and somatic angiotensin converting enzyme are of potentially different functional and structural nature, suggesting they may have different substrate specificities.

L6 ANSWER 115 OF 166 MEDLINE on STN
ACCESSION NUMBER: 94196548 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8146829
TITLE: CART and logistic regression analyses of risk factors for first dose hypotension by an ACE-inhibitor.
AUTHOR: Hasford J; Ansari H; Lehmann K
CORPORATE SOURCE: Institut fur Med. Informationsverabeitung, Biometrie und Epidemiologie, Universitat Munchen.
SOURCE: Therapie, (1993 Sep-Oct) Vol. 48, No. 5, pp. 479-82.
Journal code: 0420544. ISSN: 0040-5957.
PUB. COUNTRY: France
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199405
ENTRY DATE: Entered STN: 11 May 1994
Last Updated on STN: 11 May 1994
Entered Medline: 4 May 1994

AB Angiotensin converting enzyme inhibitors (ACEI) are established drugs for the treatment of congestive heart failure. Cases of symptomatic hypotension, especially on the first day of treatment, have been reported occasionally. The database we analysed consisted of 1,177 patients, mean age approximately 70 yrs, with congestive heart failure NYHA functional class II or III. These patients were treated and observed prospectively according to a uniform protocol, starting therapy with 2.5 mg enalapril and measuring blood pressure at hourly intervals for eight hours thereafter. 94.6% of the patients experienced no symptomatic hypotension, 4.75% moderate symptoms (e.g. dizziness, headache) and 0.59% severe symptoms (e.g. fainting, collapse, renal failure). For the analyses of risk factors a large number of baseline variables were analysed univariately to select those significant for inclusion in a multivariate stepwise logistic regression. Alternatively the CART-(classification and regression tree) technique was used. Both techniques showed diastolic blood pressure < or = 70 mmHg to be the single most significant risk factor. CART-analyses showed also pretreatment with nitrates and systolic blood pressure < or = 120 mmHg to be of prognostic relevance. Thus CART is a valuable complement when looking for prognostic factors.

L6 ANSWER 116 OF 166 MEDLINE on STN
ACCESSION NUMBER: 94047983 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8231031
TITLE: Dissociation between the course of the hemodynamic and antiproteinuric effects of angiotensin I converting enzyme inhibition.
AUTHOR: Gansevoort R T; de Zeeuw D; de Jong P E
CORPORATE SOURCE: Department of Medicine, State University Hospital, Groningen, The Netherlands.
SOURCE: Kidney international, (1993 Sep) Vol. 44, No. 3, pp. 579-84.
Journal code: 0323470. ISSN: 0085-2538.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 199312
ENTRY DATE: Entered STN: 17 Jan 1994
Last Updated on STN: 17 Jan 1994
Entered Medline: 21 Dec 1993

AB Angiotensin I converting enzyme inhibition (ACEi) has been shown to lower urinary protein excretion in human renal disease. The mechanism of this antiproteinuric effect is hypothesized to be mediated by changes in renal hemodynamics. However, clinical studies suggest that the effect on renal hemodynamics is fully established immediately after the start of treatment, whereas others show the antiproteinuric effect to reach maximum only after several weeks. To clarify this issue we studied the course of renal hemodynamics, blood pressure and proteinuria during 28 days of ACEi (enalapril 10 mg oid) in nine patients with proteinuria due to non-diabetic renal disease. The effect of ACEi on blood pressure and renal hemodynamics was already maximal within few hours after start of treatment, and remained stable thereafter: MAP was lowered with 8.6 +/- 1.9%, 10.6 +/- 2.1%, 12.8 +/- 2.3% and 12.9 +/- 2.5%, while FF fell 23.0 +/- 2.0%, 17.0 +/- 2.6%, 16.8 +/- 2.8% and 15.9 +/- 4.0% on days 1, 7, 14 and 28 of ACEi, respectively. However, the antiproteinuric effect only gradually reached its maximum on day 28. Urinary protein excretion decreased with 10.9 +/- 6.1%, 32.7 +/- 6.2%, 46.3 +/- 2.5% and 54.0 +/- 2.5% on days 1, 7, 14 and 28 of ACEi, respectively. After drug withdrawal all parameters returned towards baseline. We conclude that a dissociation occurs in the course of the ACEi induced effects on hemodynamics and urinary protein excretion.(ABSTRACT TRUNCATED AT 250 WORDS)

L6 ANSWER 117 OF 166 MEDLINE on STN
ACCESSION NUMBER: 94025650 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8212633
TITLE: [Treatment of hypertension in kidney diseases]. Lecba hypertenze u ledvinovych chorob.
AUTHOR: Horky K; Dzurik R; Fedelesova V
CORPORATE SOURCE: II. interni klinika 1. lekarske fakulty University Karlovy, Praha.
SOURCE: Vnitr ni lekar stvi, (1993 Aug) Vol. 39, No. 8, pp. 810-6. Ref: 21
Journal code: 0413602. ISSN: 0042-773X.
PUB. COUNTRY: Czech Republic
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: Czech
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199310
ENTRY DATE: Entered STN: 17 Jan 1994
Last Updated on STN: 17 Jan 1994
Entered Medline: 27 Oct 1993

AB The authors review recent therapeutic procedures in arterial hypertension associated with renal disease. Treatment of hypertension is comprehensive, it comprises non-medicamentous procedures, pharmacotherapy and in some affections also interventional and surgical therapy. Effective reduction of the blood pressure to values < or = 140/90 mmHg unequivocally retards progression of renal disease, the development of nephrosclerosis and delays the development of renal insufficiency. In medicamentous treatment of nephrogenic hypertension a wide range of conventional antihypertensive drugs is used. Their selection and dosage must be adapted to the type of the basic renal disease and the reduction of renal functions. Recently the demand has been raised that the antihypertensive drugs used should possess in addition to the blood pressure lowering effect also an additive renoprotective effect ensuing above all from diminished intraglomerular hypertension and undesirable hyperfiltration, a changed

permeability of capillary membranes due to reduction of microalbuminuria and proteinuria or restriction of proliferation procedures. These demands are met by the angiotensin I-converting enzyme (ACEI) inhibitor. If the correct dosage is used, ACEI are, due to their excellent antihypertensive action, absence of undesirable metabolic sequelae and significant renoprotective effect, drugs of the first line in nephrogenic hypertension. The authors use above all ACEI with a long-term effect, i.e. those without a SH group in the molecule. Very small doses (e.g. 2.5 mg Enalapril per day) reduce microalbuminuria and proteinuria and retard progression of nephrosclerosis also in nephropathies without systemic hypertension, e.g. in diabetic glomerulosclerosis. The renoprotective effect is manifested more markedly in initial stages of the disease.(ABSTRACT TRUNCATED AT 250 WORDS)

L6 ANSWER 118 OF 166 MEDLINE on STN
ACCESSION NUMBER: 93252064 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8387427
TITLE: Pharmacokinetics and pharmacodynamics of quinaprilat after low dose quinapril in patients with terminal renal failure.
AUTHOR: Wolter K; Fritschka E
CORPORATE SOURCE: Department of Internal Medicine, University Hospital Essen, Germany.
SOURCE: European journal of clinical pharmacology, (1993) Vol. 44 Suppl 1, pp. S53-6.
Journal code: 1256165. ISSN: 0031-6970.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199306
ENTRY DATE: Entered STN: 18 Jun 1993
Last Updated on STN: 18 Jun 1993
Entered Medline: 9 Jun 1993

AB The pharmacokinetics and pharmacodynamics of the ACE inhibitor quinaprilat have been studied in six chronic haemodialysis (HD) patients and in six patients undergoing continuous ambulatory peritoneal dialysis (CAPD) after a single oral dose of 2.5 mg quinapril. Mean tmax and Cmax values (SEM) for quinaprilat in interdialytic HD patients were 4.0 (0) h and 84 (8.4) ng.ml-1 respectively, and they did not differ significantly from those in CAPD patients (4.7 (0.7) h and 64 (5.7) ng.ml-1). Elimination half lives were 30 (10.1) h (HD) and 34 (7.3) h (CAPD). Cmax, tmax, t1/2, and AUC were increased and CL was decreased compared to data reported previously after giving 2.5 mg to healthy subjects. Peritoneal clearance was calculated as 0.1 (0.1) ml.min-1, thus less than 0.5% of the dose were removed within 24 h by CAPD. ACE activity was suppressed by more than 93% between 4 and 24 h postdose ($P < 0.001$). It decreased in both groups with increasing plasma quinaprilat levels. Angiotensin II concentration compared to baseline was significantly decreased at 4 hours (-30.4 +/- 10%) and 24 h (-30 +/- 9.9%) ($P < 0.05$, $n = 11$), while active plasma renin concentration was still significantly increased at 48 h postdose (+ 60.2 +/- 14.5%, $P < 0.01$). Mean arterial pressure 24 h postdose was significantly ($P < 0.05$) decreased in HD (-12 mmHg) and CAPD patients (-20 mm Hg). Only two patients reported unwanted effects (fatigue, dizziness, nausea, and weakness). In conclusion, due to its long lasting effect on ACE activity and on blood pressure in terminal renal failure a starting dose of quinapril 2.5 mg o.d. may be used in hypertensive HD and CAPD patients.

L6 ANSWER 119 OF 166 MEDLINE on STN
ACCESSION NUMBER: 93086027 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1280705
TITLE: Renal effects of alacepril in essential hypertension.

AUTHOR: Tomita K; Nonoguchi H; Terada Y; Marumo F
CORPORATE SOURCE: Second Department of Internal Medicine, Tokyo Medical and Dental University, Japan.
SOURCE: Journal of cardiovascular pharmacology, (1992 Oct) Vol. 20, No. 4, pp. 520-4.
Journal code: 7902492. ISSN: 0160-2446.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199301
ENTRY DATE: Entered STN: 29 Jan 1993
Last Updated on STN: 29 Jan 1996
Entered Medline: 7 Jan 1993

AB Short-term effects of alacepril, an angiotensin-converting enzyme inhibitor (ACEI), on renal function and hemodynamics were investigated in 10 hypertensive subjects (aged 55.7 +/- 9.5 years, mean +/- SD). Renal plasma flow (RPF) and glomerular filtration rate (GFR) were examined before and after 12-week administration of alacepril, by [131I]hippuran and [99mTc]DTPA, respectively. Alacepril (50 mg/day) caused a significant decrease in both systolic and diastolic blood pressure (SBP and DBP, from 161 +/- 8 to 140 +/- 10 mm Hg and from 100 +/- 3 to 90 +/- 5 mm Hg, respectively). Alacepril increased GFR (from 63.4 +/- 22.2 to 69.1 +/- 22.1 ml/min/1.73 m2, p less than 0.05) without changing RPF (from 438 +/- 194 to 432 +/- 148 ml/min/1.73 m2, p greater than 0.05). Serum creatinine and electrolytes were not changed by alacepril administration. These data show that short-term alacepril administration improves renal function, probably owing to relaxation of renal vasoconstriction.

=> dis ibib abs l6 100-109

L6 ANSWER 100 OF 166 MEDLINE on STN
ACCESSION NUMBER: 95350847 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7624949
TITLE: Combined antagonism of endothelin A/B receptors links endothelin to vasoconstriction whereas angiotensin II effects fibrosis. Studies in chronic cyclosporine nephrotoxicity in rats.
AUTHOR: Kon V; Hunley T E; Fogo A
CORPORATE SOURCE: Department of Pediatrics, Vanderbilt University School of Medicine, Nashville, Tennessee 37232-2584, USA.
CONTRACT NUMBER: DK42131 (NIDDK)
DK42159 (NIDDK)
DK44757 (NIDDK)
SOURCE: Transplantation, (1995 Jul 15) Vol. 60, No. 1, pp. 89-95.
Journal code: 0132144. ISSN: 0041-1337.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199508
ENTRY DATE: Entered STN: 11 Sep 1995
Last Updated on STN: 3 Feb 1997
Entered Medline: 31 Aug 1995

AB Both functional and structural damage characterize nephrotoxicity due to cyclosporine (CsA) with accumulating evidence for dissociation of mechanisms that lead to each of these processes. We studied the role of endothelin (Et) and angiotensin II (AII), since each of these peptides can modulate vasoconstriction as well as parenchymal destruction. Salt-depleted rats were treated with daily CsA (15 mg/kg s.c.) for 5 weeks (group 1, CsA, n = 13). Separate groups of CsA-treated rats received

either a combined antagonist of both EtA/EtB receptors (group 2, CsA+aEtA/B, 100 mg/kg/day p.o., n = 6) or angiotensin I-converting enzyme inhibitor (group 3, CsA+ACEI, enalapril 200 mg/L drinking water, n = 8). Glomerular filtration rate (GFR) was assessed by creatinine clearance (Ccr) in conscious rats at 3 and 5 weeks. At 3 weeks, serum creatinine was 1.5 +/- 0.1 mg/dl in group 1 rats, 1.2 +/- 0.2 mg/dl in group 2 rats (P < 0.05 vs. CsA), and 2.3 +/- 0.8 mg/dl in group 3 rats. Ccr was 0.87 +/- 0.08 ml/min in group 1. In group 2, GFR was remarkably preserved (1.14 +/- 0.11 ml/min, P < 0.05 vs. group 1). By contrast, GFR in group 3 rats was lower (0.31 +/- 0.08 ml/min) than either aEtA/B-treated or even CsA-treated rats (P < 0.0005 vs. group 1, P < 0.0005 vs. group 2). At 5 weeks, the same pattern emerged; serum creatinine was 2.5 +/- 0.2 mg/dl in group 1, 1.2 +/- 0.1 in group 2 (P < 0.0005 vs. CsA), and 3.4 +/- 0.9 in group 3 (P < 0.025 vs. CsA+aEtA/B). Ccr had decreased dramatically in CsA-treated rats to 0.18 +/- 0.03 ml/min. GFR was preserved in CsA+aEtA/B rats (0.51 +/- 0.03 ml/min, P < 0.0005 vs. group 1), while profound hypofiltration was apparent in CsA+ACEI rats (0.12 +/- 0.03 ml/min, P < 0.0005 vs. group 2). In salt-depleted control animals, GFR was 0.62 +/- 0.02 ml/min. Despite striking functional preservation in response to antagonism of Et receptors, tubular vacuolization/dilatation, as well as arteriolopathy, was not different among the CsA-treated groups. Tubulointerstitial fibrosis was also not different between CsA and CsA+aEtA/B rats (on a 0-4 scale, 1.05 +/- 0.14 vs. 0.87 +/- 0.14, P = NS). In contrast, both tubular vacuolization/dilatation and interstitial fibrosis were significantly greater in all CsA-treated groups compared with salt-depleted controls. However, in the CsA+ACEI group that had the most severe hypofiltration at each time point, tubulointerstitial fibrosis was 0.69 +/- 0.06 (P < 0.05 vs. CsA).(ABSTRACT TRUNCATED AT 400 WORDS)

L6 ANSWER 101 OF 166 MEDLINE on STN
ACCESSION NUMBER: 95349779 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7623991
TITLE: Additive antiproteinuric effect of ACE inhibition and a low-protein diet in human renal disease.
AUTHOR: Gansevoort R T; de Zeeuw D; de Jong P E
CORPORATE SOURCE: Groningen Institute for Drug Studies (GIDS), Department of Medicine, State University Hospital, The Netherlands.
SOURCE: Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association, (1995) Vol. 10, No. 4, pp. 497-504.
Journal code: 8706402. ISSN: 0931-0509.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: (CLINICAL TRIAL)
(CONTROLLED CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199508
ENTRY DATE: Entered STN: 11 Sep 1995
Last Updated on STN: 3 Mar 2000
Entered Medline: 29 Aug 1995

AB Both ACEi and a low-protein diet (LPD) are reported to reduce urinary protein excretion in patients with stable non-diabetic renal disease. To test whether the combination of both may have an additive antiproteinuric effect, we studied the effects of single treatment with ACEi (10 mg enalapril o.d.), LPD (target, 50% reduction in protein intake), and the combination of both in 14 of such patients with stable proteinuria exceeding 3 g per day. Baseline measurements were performed while patients were on a normal protein diet (NPD). In group A (n = 7), first the effects of a LPD were investigated, whereafter the effects of addition of ACEi to LPD

were studied. In group B (n = 7), first the effects of ACEi were investigated, whereafter the effects of addition of a LPD to ACEi were studied. Each treatment period lasted 2 months. LPD decreased proteinuria with 17% in patients without ACEi treatment (group A), and similarly with 19% in patients with ACEi treatment (group B). The antiproteinuric response obtained with the LPD in individual patients ranged from -63% to +1%. This variation is at least partly explained by interindividual differences in diet compliance, since the antiproteinuric effect of the LPD was found to correlate with the achieved reduction in protein intake ($r = 0.58$, $P < 0.05$). ACEi lowered proteinuria with 32% during the NPD (group B), and similarly with 43% during the LPD (group A).(ABSTRACT TRUNCATED AT 250 WORDS)

L6 ANSWER 102 OF 166 MEDLINE on STN
ACCESSION NUMBER: 95282391 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7762186
TITLE: [Ineffectiveness of ACE inhibitors (enalapril) on glomerular damage in rats after a 5/6 nephrectomy and a high-salt diet].
Neucinnost ACEI (enalaprilu) na prubeh glomerularniho poskozeni u krys po 5/6 nefrektomii, krmenych vysokoslanou dietou.
AUTHOR: Cervenka L; Heller J; Hellerova S
CORPORATE SOURCE: Pracoviste preventivni kardiologie IKEM, Praha.
SOURCE: Vnitr ni lekar stvi, (1995 Apr) Vol. 41, No. 4, pp. 230-4.
Journal code: 0413602. ISSN: 0042-773X.
PUB. COUNTRY: Czech Republic
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Czech
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199506
ENTRY DATE: Entered STN: 7 Jul 1995
Last Updated on STN: 7 Jul 1995
Entered Medline: 27 Jun 1995
AB Wistar rats with surgically removed 5/6 of renal parenchyma were fed either standard (0.35% salt content) or a high-salt (2%) diet. Half of the animals of each group drunk plain water while the other half was provided water enriched with the angiotensin-converting enzyme inhibitor enalapril (ENA) at a dose of 5 mg/kg/day. In rats receiving standard diet, ENA had a significant inhibitory effect on the consequences of ablation: the rats had normal blood pressure, low proteinuria, and high endogenous creatinine clearance compared to water-drinking controls. The high-salt diet significantly enhanced the sequelae of ablation: a high blood pressure and proteinuria, low clearance, which ENA was unable to prevent in these animals. No plausible explanation for the absence of ENA's beneficial effect is available: one can speculate that, under conditions of high-salt intake, the activity of the renin-angiotensin system is suppressed leaving no place for ENA to exert its effect. We also believe that the highly adverse effect of a high-salt diet in chronic renal failure is due to growth factors other than angiotensin II.

L6 ANSWER 103 OF 166 MEDLINE on STN
ACCESSION NUMBER: 95152007 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7849255
TITLE: Evidence that an angiotensin-converting enzyme inhibitor has a different effect on glomerular injury according to the different phase of the disease at which the treatment is started.
AUTHOR: Perico N; Amuchastegui S C; Colosio V; Sonzogni G; Bertani T; Remuzzi G
CORPORATE SOURCE: Mario Negri Institute for Pharmacological Research, Bergamo, Italy.
SOURCE: Journal of the American Society of Nephrology : JASN, (1994

Oct) Vol. 5, No. 4, pp. 1139-46.
Journal code: 9013836. ISSN: 1046-6673.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199503
ENTRY DATE: Entered STN: 22 Mar 1995
Last Updated on STN: 22 Mar 1995
Entered Medline: 16 Mar 1995

AB In rats with streptozotocin-induced diabetes, the effect of an angiotensin-converting enzyme (ACE) inhibitor on the evolution of glomerular injury according to the time at which the treatment is started with respect to the onset of the disease was studied. Three groups of animals were used, a control Group 1 and two groups of diabetic rats treated with insulin (Groups 2 and 3). The latter were monitored until urinary protein excretion reached 40 to 50 mg/24 h (on average, 23 wk after the induction of the diabetes). At this time, Group 2 continued to receive insulin alone, whereas Group 3 was also given the ACE inhibitor moexipril for 8 more wk. Untreated diabetic rats showed a moderate increase in systolic blood pressure that was normalized by moexipril administration. Urinary protein excretion progressively increased during the 8-wk follow-up in untreated diabetics that, at the end of the study, developed moderate glomerular sclerosis. Moexipril treatment lowered urinary protein excretion to a normal range and completely prevented glomerular injury. Three other groups of rats were similarly treated, except that moexipril treatment was started later on (when proteinuria reached 100 to 200 mg/24 h, on average, 32 wk after the induction of diabetes), and were monitored for another 8 wk. Untreated and treated diabetics had comparable blood glucose levels throughout. Systolic blood pressure, significantly increased in untreated diabetic rats, was effectively controlled by moexipril administration.(ABSTRACT TRUNCATED AT 250 WORDS)

L6 ANSWER 104 OF 166 MEDLINE on STN
ACCESSION NUMBER: 95147993 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7845479
TITLE: Effects of enalapril and hydrochlorothiazide on the salt-induced cardiac and renal hypertrophy in normotensive rats.
AUTHOR: Mervaala E M; Laakso J; Vapaatalo H; Karppanen H
CORPORATE SOURCE: Department of Pharmacology and Toxicology, University of Helsinki, Finland.
SOURCE: Naunyn-Schmiedeberg's archives of pharmacology, (1994 Oct) Vol. 350, No. 4, pp. 416-25.
Journal code: 0326264. ISSN: 0028-1298.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199503
ENTRY DATE: Entered STN: 16 Mar 1995
Last Updated on STN: 3 Mar 2000
Entered Medline: 7 Mar 1995

AB Recent studies have shown that, not only in hypertensive animals but even in normotensive rats, dietary salt (sodium chloride) produces a dose-related increase in the left ventricular and renal mass. In the present study the effects of the angiotensin converting enzyme inhibitor (ACEI) enalapril and the thiazide-type diuretic, hydrochlorothiazide, on the development of the salt-induced left ventricular and kidney hypertrophy were examined in normotensive Wistar-Kyoto and Wistar rats. A high intake of sodium chloride (6% of the dry weight of the chow to mimic the level found in many human food items) during eight weeks produced a marked increase in the mass of the left

ventricle and the kidneys in both rat strains with little or no effect on blood pressure. The cardiac hypertrophy correlated strongly with the renal hypertrophy. These salt-induced changes in the heart and in the kidneys were completely blocked by hydrochlorothiazide, while enalapril was devoid of any significant effects during the high-salt diet. However, during a low-salt diet enalapril, but not hydrochlorothiazide, effectively lowered the blood pressure and decreased the left ventricular mass of the normotensive rats. There was a 3- to 4-fold increase in the urinary excretion of calcium during the high intake of sodium chloride. Hydrochlorothiazide decreased the urinary excretion of calcium even during the low salt diet, and it completely blocked the salt-induced hypercalciuria. Enalapril had no significant effect on the urinary calcium excretion. During the low-salt diet hydrochlorothiazide increased the calcium and decreased the potassium concentration in the heart while enalapril increased the phosphorus concentration. In conclusion, a high intake of sodium chloride produced hypertrophy both in the heart and in the kidneys, even in the absence of a rise in blood pressure. Salt also remarkably increased the urinary calcium excretion. These harmful effects of salt were blocked by the thiazide diuretic hydrochlorothiazide but not by the ACEI enalapril. However, this study does not allow to make any direct comparison between the effects of enalapril and hydrochlorothiazide.

L6 ANSWER 105 OF 166 MEDLINE on STN
ACCESSION NUMBER: 95114361 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7814850
TITLE: Mechanistic analysis of renal protection by angiotensin converting enzyme inhibitor in Dahl salt-sensitive rats.
AUTHOR: Hirawa N; Uehara Y; Kawabata Y; Ohshima N; Ono H; Nagata T; Gomi T; Ikeda T; Goto A; Yagi S; +
CORPORATE SOURCE: Department of Nephrology, Kantoh-Teishin Hospital, Tokyo, Japan.
SOURCE: Journal of hypertension, (1994 Aug) Vol. 12, No. 8, pp. 909-18.
Journal code: 8306882. ISSN: 0263-6352.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199502
ENTRY DATE: Entered STN: 17 Feb 1995
Last Updated on STN: 6 Feb 1998
Entered Medline: 8 Feb 1995

AB OBJECTIVE: To investigate whether and how renin-angiotensin inhibition attenuates renal injury seen in salt-induced hypertension in Dahl salt-sensitive (Dahl-S) rats. METHODS: Dahl-S rats fed a high-salt (4% sodium chloride) diet for 6 weeks were treated with the angiotensin converting enzyme (ACE) inhibitor alacepril or the angiotensin receptor antagonist losartan for 4 weeks. Functional and morphological alterations in the kidney were investigated. RESULTS: Alacepril decreased systolic blood pressure (SBP). This SBP reduction was associated with the attenuation of cardiac and aortic wall hypertrophy and that of proteinuria and urinary N-acetyl-beta-D-glucosaminidase excretion. Kidney injuries, e.g. glomerular, arterial and tubular damage, were improved with alacepril treatment. Losartan decreased SBP to the same extent as alacepril , but neither renal function nor morphological structure was improved as was the case with alacepril. The response of the renal eicosanoid system to alacepril was inadequate, but cyclic GMP excretion, an indicator of nitric oxide formation, was significantly enhanced and lipid peroxidation in the kidney was

decreased. CONCLUSIONS: The beneficial effects of ACE inhibition on the renal injury in Dahl-S rats outrange those induced by the receptor antagonism. This might be due to multiple factors including an increased vasodepressor eicosanoid system, enhanced nitric oxide formation and possible inhibition of oxygen radical generation in the injured renal tissues.

L6 ANSWER 106 OF 166 MEDLINE on STN
ACCESSION NUMBER: 95088006 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7995636
TITLE: Long-term infusion of kallikrein attenuates renal injury in Dahl salt-sensitive rats.
AUTHOR: Uehara Y; Hirawa N; Kawabata Y; Suzuki T; Ohshima N; Oka K; Ikeda T; Goto A; Toyo-oka T; Kizuki K; +
CORPORATE SOURCE: Second Department of Medicine, University of Tokyo, Japan.
SOURCE: Hypertension, (1994 Dec) Vol. 24, No. 6, pp. 770-8.
Journal code: 7906255. ISSN: 0194-911X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199501
ENTRY DATE: Entered STN: 26 Jan 1995
Last Updated on STN: 3 Mar 2000
Entered Medline: 18 Jan 1995

AB We investigated whether long-term infusion of kallikrein would attenuate renal injury in salt-induced hypertension in Dahl salt-sensitive rats. A subdepressor dose of purified rat urinary kallikrein (700 ng/d IV) was infused by osmotic minipump for 4 weeks in male Dahl salt-sensitive rats fed a high salt (2% NaCl) diet. This dose did not affect the time-dependent elevation of blood pressure; however, urinary protein excretion was significantly decreased, and glomerular filtration rate was increased. These beneficial effects were reflected morphologically by an attenuation of glomerulosclerotic lesions and tubular injury seen in the hypertensive Dahl salt-sensitive rats. Kallikrein infusion increased urinary excretion of bradykinin and stimulated excretion of cyclic GMP, suggesting that the kallikrein-kinin-prostaglandin and nitric oxide axes were enhanced by rat urinary kallikrein infusion. The alterations induced by kallikrein infusion were potentiated by the concomitant administration of the angiotensin-converting enzyme inhibitor alacepril. These studies indicated that long-term replacement with rat tissue kallikrein attenuates renal injury in hypertensive Dahl salt-sensitive rats.

L6 ANSWER 107 OF 166 MEDLINE on STN
ACCESSION NUMBER: 95080015 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7527326
TITLE: Quinapril. A reappraisal of its pharmacology and therapeutic efficacy in cardiovascular disorders.
AUTHOR: Plosker G L; Sorkin E M
CORPORATE SOURCE: Adis International Limited, Auckland, New Zealand.
SOURCE: Drugs, (1994 Aug) Vol. 48, No. 2, pp. 227-52. Ref: 153
Journal code: 7600076. ISSN: 0012-6667.
PUB. COUNTRY: New Zealand
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199501
ENTRY DATE: Entered STN: 24 Jan 1995
Last Updated on STN: 29 Jan 1996

Entered Medline: 10 Jan 1995

AB Following systemic absorption, quinapril is converted by de-esterification to quinaprilat (the active diacid metabolite), an inhibitor of angiotensin converting enzyme (ACE). Pharmacodynamic studies in animals indicate inhibition of ACE both in plasma and at tissue sites, such as the arterial wall and heart, following administration of quinapril. Tissue ACE inhibition may be an important component of the mechanism of action of quinapril (and other ACE inhibitors) in achieving favourable effects in cardiovascular disorders. Quinaprilat has a short elimination half-life (approximately 2 hours), but binds potently to and dissociates slowly from ACE, thus allowing once or twice daily administration of quinapril in the treatment of patients with hypertension or congestive heart failure. Quinapril 10 to 40 mg/day has achieved adequate control of blood pressure in most patients with essential hypertension in clinical trials. Some patients required quinapril dosages up to 80 mg/day and/or concomitant diuretic therapy. Titrating quinapril dosages from 10 to 40 mg/day increased response rates without increasing the incidence or severity of adverse events. Addition of hydrochlorothiazide to quinapril therapy improved response rates by approximately 10 to 20% in patients with hypertension. In general, blood pressure control with quinapril monotherapy was similar to that achieved with enalapril or other standard antihypertensive agents in comparative trials. Quinapril < or = 40 mg/day improved exercise tolerance, reduced the severity and frequency of symptoms, and improved functional (New York Heart Association) class in most clinical studies of patients with congestive heart failure. In addition, beneficial haemodynamic and echocardiographic changes achieved with quinapril were maintained for up to 1 year with continued administration to such patients, but its effect on survival in patients with congestive heart failure has not been reported. The tolerability profile of quinapril is broadly similar to that of other ACE inhibitors; pooled data from clinical trials indicated that 12% of patients with hypertension or congestive heart failure receiving quinapril experienced a treatment-related adverse effects compared with 15% of enalapril recipients and 16% of captopril recipients. Thus, quinapril has clearly established a role as an effective and well tolerated alternative to other ACE inhibitors for the treatment of hypertension and congestive heart failure. While effects of quinapril on survival of patients with congestive heart failure have not been determined, large intervention studies have demonstrated improved mortality rates with other ACE inhibitors. Further studies, including a large ongoing trial of normotensive patients with coronary artery disease but normal left ventricular function, may also establish a role for quinapril in treating patients with ischaemic heart disease.

L6 ANSWER 108 OF 166 MEDLINE on STN

ACCESSION NUMBER:	95076971 MEDLINE
DOCUMENT NUMBER:	PubMed ID: 7985667
TITLE:	Lack of efficacy of angiotensin-converting enzyme inhibitors in reducing interdialytic weight gain.
AUTHOR:	Bastani B; Redington J
CORPORATE SOURCE:	Division of Nephrology, St Louis University Medical Center, MO.
SOURCE:	American journal of kidney diseases : the official journal of the National Kidney Foundation, (1994 Dec) Vol. 24, No. 6, pp. 907-11. Journal code: 8110075. ISSN: 0272-6386.
PUB. COUNTRY:	United States
DOCUMENT TYPE:	Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:	English
FILE SEGMENT:	Priority Journals
ENTRY MONTH:	199501
ENTRY DATE:	Entered STN: 16 Jan 1995 Last Updated on STN: 16 Jan 1995 Entered Medline: 5 Jan 1995

AB Angiotensin-converting enzyme inhibitors (ACEIs) have been suggested to reduce interdialytic fluid weight gain, presumably via suppression of the dipsogenic angiotensin II. We retrospectively studied 25 (76% black) chronic hemodialysis patients who received ACEIs for blood pressure control. The mean arterial blood pressure decreased from 115.4 +/- 10.4 mm Hg to 112.7 +/- 9.0 mm Hg (mean +/- SD; P = NS) and there was no change in the interdialytic weight gain (3.74 +/- 1.5 kg v 3.72 +/- 1.5 kg; P = NS). Only 10 (40%) patients had some reduction in their interdialytic weight gain; in four of them the reduction was more than 20% of the pre-ACEI weight gain. When nine patients who had no decline in blood pressure were excluded due to possible noncompliance, the mean arterial blood pressure in the remaining 16 patients (75% black) declined from 119.3 +/- 9.9 mm Hg to 111.6 +/- 9.9 mm Hg (P < 0.0001), but there was no change in the interdialytic fluid weight gain (3.7 +/- 1.4 kg v 3.8 +/- 1.4 kg; P = NS). There was no correlation between age, race, etiology of renal failure, or blood pressure response and change in the interdialytic weight gain after ACEI treatment. Our results do not support the previous report that ACEIs significantly decrease the interdialytic weight gain in chronic hemodialysis patients. The multifactorial nature of excessive fluid intake in the hemodialysis patients and the differences in patient population and study design may account for this discrepancy.

L6 ANSWER 109 OF 166 MEDLINE on STN
ACCESSION NUMBER: 95075036 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7527095
TITLE: Compared properties of trandolapril, enalapril, and their diacid metabolites.
AUTHOR: Chevillard C; Jouquey S; Bree F; Mathieu M N; Stepniewski J P; Tillement J P; Hamon G; Corvol P
CORPORATE SOURCE: INSERM U300, Montpellier, France.
SOURCE: Journal of cardiovascular pharmacology, (1994) Vol. 23 Suppl 4, pp. S11-5.
Journal code: 7902492. ISSN: 0160-2446.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199501
ENTRY DATE: Entered STN: 16 Jan 1995
Last Updated on STN: 29 Jan 1996
Entered Medline: 5 Jan 1995

AB The effects of 14-day trandolapril or enalapril treatment of spontaneously hypertensive rats (SHRs) were studied on blood pressure and angiotensin-converting enzyme (ACE) activity measured ex vivo in various organs. Both ACE inhibitors caused dose-dependent decreases in blood pressure and ACE activity, trandolapril being 30- and 400- to 1,000-fold more active than enalapril on blood pressure and ACE activity, respectively. However, comparison of ACE inhibitory activities of the diacid forms of trandolapril and enalapril, i.e., trandolaprilat and enalaprilat, measured in vitro on various tissues, showed that trandolaprilat was only three- to fivefold more active than enalaprilat. To understand the reasons for such discrepancies between ex vivo effects of ACE inhibitors and in vitro actions of their diacid metabolites, we measured the lipophilicities of the compounds and investigated the possibility that trandolapril could display an ACE inhibitory effect by itself. Trandolaprilat was found to be far more lipophilic than enalaprilat, as shown by reverse-phase high-performance liquid chromatography studies performed at pH 7.4 (log kw7.4 = 1.487 vs. 0.108). In addition, trandolapril was practically as active in vitro as its diacid metabolite (IC50 = 2.5 vs. 1.35 nM) in inhibiting ACE activity in the aorta, whereas enalapril was practically devoid of any effect (IC50 = 240 nM). Measurements of relative affinities of inhibitors or metabolites for purified human renal ACE showed that trandolapril displayed

about 20% of the affinity of its diacid metabolite (IC50 = 15 vs. 3.2 nM); enalaprilat affinity (34 nM) was within the same range as those of trandolapril and trandolaprilat, whereas enalapril displayed a very low affinity for the purified enzyme (IC50 = 50 microM).(ABSTRACT TRUNCATED AT 250 WORDS)

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L6 ANSWER 90 OF 166 MEDLINE on STN
ACCESSION NUMBER: 96336613 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8743511
TITLE: Antihypertensive agents and renal protection: calcium channel blockers.
AUTHOR: Saruta T; Kanno Y; Hayashi K; Konishi K
CORPORATE SOURCE: Department of Internal Medicine, School of Medicine, Keio University, Tokyo, Japan.
SOURCE: Kidney international. Supplement, (1996 Jun) Vol. 55, pp. S52-6.
Journal code: 7508622. ISSN: 0098-6577.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199611
ENTRY DATE: Entered STN: 19 Dec 1996
Last Updated on STN: 19 Dec 1996
Entered Medline: 20 Nov 1996

AB This study defines the nature of the renal protective effects of calcium channel blockers (Ca blockers) and the effects of the Ca blocker, amlodipine, compared to those of the angiotensin-converting enzyme inhibitor (ACEI), enalapril, on the progression of renal injury in 5/6 nephrectomized spontaneously hypertensive rats (SHR) fed a high-salt diet. Furthermore, we studied the effects of various Ca blockers on the glomerular afferent and efferent arterioles using the isolated perfused hydronephrotic kidneys of six-week-old male Sprague-Dawley rats. In the first study, forty 6-week-old male SHRs which underwent 5/6 nephrectomy were equally divided into five groups. One group received no therapy. In two groups, therapy was started at four weeks post-nephrectomy, one with amlodipine and the other with enalapril. In the remaining two groups, amlodipine or enalapril therapy was started at eight weeks postnephrectomy. Amlodipine was more effective than enalapril in reducing proteinuria and glomerulosclerosis in the group that was started on drug therapy eight weeks after surgery. In the second study, at concentrations of 10(-6) to 10(-9) M, nifedipine, nicardipine and amlodipine dilated the afferent, but not the efferent, arteriole preconstricted with angiotensin II. On the other hand, efonidipine and manidipine clearly dilated angiotensin II-induced constriction of both the afferent and efferent arterioles. These results indicated that Ca blockers are effective at reducing renal injury in 5/6 nephrectomized SHR, and that they are more effective than ACEI in advanced stages of renal injury. The observation that only certain Ca blockers can dilate the efferent arteriole suggests that the renal protective effect of Ca blockers is not necessarily dependent on the dilation of the efferent arterioles.

L6 ANSWER 91 OF 166 MEDLINE on STN
ACCESSION NUMBER: 96313697 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8697492
TITLE: [Comparison of the effects of a low protein diet and angiotensin converting enzyme inhibitors on renal insufficiency in hypertensive rats].
Srovnani ucinku diety o nizkem obsahu proteinu a

angiotenzin konvertujiciho enzymu (ACEI) na prubeh renalni insuficience hypertenznich krys.
AUTHOR: Cervenka L; Heller J
CORPORATE SOURCE: Pracoviste preventivni kardiologie IKEM, Praha.
SOURCE: Casopis lekar u c eskych, (1996 May 15) Vol. 135, No. 10, pp. 305-7.
Journal code: 0004743. ISSN: 0008-7335.
PUB. COUNTRY: Czech Republic
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Czech
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199609
ENTRY DATE: Entered STN: 12 Sep 1996
Last Updated on STN: 12 Sep 1996
Entered Medline: 4 Sep 1996

AB BACKGROUND. It is known that hypertension to aggravate the course of chronic renal insufficiency (CRI). It is too know the beneficial effect of the angiotensin-converting enzyme inhibitors (ACEI) and the low-protein diet. In this study, the effect of a low protein diet on the course of CRI was compared with that of administration of enalapril (ENA), an ACEI. METHODS AND RESULTS. A new model of genetic hypertension, the Prague Hypertensive Rat (PHR) was used. In rats just after weaning, 5/6 of renal parenchyma were removed surgically (5/6NX). The rats were observed for 8 weeks after 5/6NX. The animals were fed either a normal rat chow containing 23% of protein, or a low-protein diet containing only 6% protein. Control groups drank tap water, experimental groups received water containing ENA at a dose of 5 mg/kg BW. The rats on normal diet drinking water had the highest levels of blood pressure (200 +/- 4.3 mm Hg), proteinuria (56.2 +/- 14.6 mg/24 hours) and heaviest kidney remnants i.e. highest compensatory hypertrophy (2352 +/- 239.4 mg). Both ENA and low-protein diet significantly improved these functions to the same extent. However, a combination of low-protein diet with ENA had no further beneficial effect as against any of these manoeuvres alone. CONCLUSIONS. We assume every manoeuvre (low-protein diet and enalapril) exerts a maximal beneficial effect per se: the mechanism of this effect is highly speculative: inhibition of growth factors seems to be the most logical explanation. ACEIs are known to inhibit the production of angiotensin II, low-protein diet should inhibit transforming growth factor beta.

L6 ANSWER 92 OF 166 MEDLINE on STN
ACCESSION NUMBER: 96311220 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8723355
TITLE: Comparison of the effects of a low-protein diet with the effects of a converting enzyme inhibitor on the progression of renal insufficiency in hypertensive rats.
AUTHOR: Cervenka L; Heller J
CORPORATE SOURCE: Department of Preventive Cardiology, Institute for Clinical and Experimental Medicine, Prague, Czech Republic.
SOURCE: Renal failure, (1996 Mar) Vol. 18, No. 2, pp. 173-80.
Journal code: 8701128. ISSN: 0886-022X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199610
ENTRY DATE: Entered STN: 25 Oct 1996
Last Updated on STN: 25 Oct 1996
Entered Medline: 17 Oct 1996

AB The beneficial effects of a low-protein diet vs. angiotensin-converting enzyme inhibitor (ACEI, enalapril) on the course of ablation nephropathy (5/6 nephrectomy, 5/6NX) were compared in a new strain of genetic hypertensive rats, the Prague hypertensive rat (PHR).

Both maneuvers were followed by a significant drop in proteinuria (1.27 and 8.8 vs. 56.2 mg/24 hod, p < 0.001, low-protein diet vs. ACEI vs. untreated), plasma levels of creatinine (175.3 and 177.1 vs. 245.3 mumol/L, p < 0.001) and urea (7.95 and 13.51 vs. 37.6 mmol/L, p < 0.001). Endogenous creatinine clearance was higher after both low-protein diet and ACEI than without them (134.6 and 127.8 vs. 56.7 microL/min/100 g BW, p < 0.001). Both maneuvers had a similar beneficial effect: no additional amelioration was observed with a combination of both low-protein diet and ACEI. Compared to normotensive Wistar rats, the results were quite similar in PHR except the blood pressure values; hypertension had no substantial effect on the course of 5/6NX or on the beneficial action of both low-protein diet and ACEI.

L6 ANSWER 93 OF 166 MEDLINE on STN
ACCESSION NUMBER: 96289273 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8764318
TITLE: Effect of dietary protein and enalapril on proximal tubular delivery and absorption of albumin in nephrotic rats.
AUTHOR: Fitzgibbon W R; Webster S K; Imamura A; Ploth D W; Hutchison F N
CORPORATE SOURCE: Department of Medicine, Medical University of South Carolina, Charleston 29425, USA.
SOURCE: The American journal of physiology, (1996 Jun) Vol. 270, No. 6 Pt 2, pp. F986-96.
Journal code: 0370511. ISSN: 0002-9513.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199609
ENTRY DATE: Entered STN: 24 Sep 1996
Last Updated on STN: 24 Sep 1996
Entered Medline: 19 Sep 1996

AB In passive Heymann nephritis (PHN), angiotensin-converting enzyme inhibition (ACEI) or a low dietary protein intake decreases albuminuria (UAlbV). Although this reduction in albuminuria appears to result from an improvement in glomerular permselectivity, the effect of these treatments on albumin permeation and absorption by the nephron has not been clarified. This study used micropuncture techniques to examine the effect of these two treatments on albumin permeation (by measuring the delivery of albumin to the proximal tubule) and the tubular absorption of albumin. PHN rats (12-18 days after injection of FX1A) were switched from 23% to either 40% protein diet (HP), 40% protein diet and concomitantly treated with enalapril (40 mg.kg-1.day-1) (HPE), or to 8% (LP) protein diet for 4-6 days. Although left kidney glomerular filtration rate (GFR) did not differ among the groups, UAlbV from the left kidney in LP and HPE was only 20-40% of that observed for the HP group. In protocol 1, the fractional recovery of albumin (FRAlb) in urine was calculated following injection of artificial tubular fluid containing [14C]inulin and 125I-labeled albumin into the earliest identifiable proximal loops. There were no differences in FRAlb among the three groups. In protocol 2, timed quantitative collections of tubular fluid were obtained from proximal tubular loops. The rate of albumin delivery to the earliest accessible loops of the proximal tubule was significantly lower for the LP and HPE groups compared with the HP group. For each group, albumin concentration corrected for water absorption was not altered along the proximal tubule. The data indicate that alterations of dietary protein intake or ACEI treatment results in large changes in the delivery of albumin at the proximal tubule that could singularly account for the changes in urinary albumin excretion.

L6 ANSWER 94 OF 166 MEDLINE on STN
ACCESSION NUMBER: 96223532 MEDLINE

DOCUMENT NUMBER: PubMed ID: 8659493
TITLE: In hereditary nephritis angiotensin-converting enzyme inhibition decreases proteinuria and may slow the rate of progression.
AUTHOR: Cohen E P; Lemann J Jr
CORPORATE SOURCE: Department of Medicine, Medical College of Wisconsin, Froedtert Memorial Lutheran Hospital, Milwaukee 53226, USA.
CONTRACT NUMBER: CA 24652 (NCI)
SOURCE: American journal of kidney diseases : the official journal of the National Kidney Foundation, (1996 Feb) Vol. 27, No. 2, pp. 199-203.
Journal code: 8110075. ISSN: 0272-6386.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CASE REPORTS)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199608
ENTRY DATE: Entered STN: 8 Aug 1996
Last Updated on STN: 8 Aug 1996
Entered Medline: 1 Aug 1996

AB The hereditary nephritides are often progressive, resulting in kidney failure and the need for renal replacement therapy. There is no currently known beneficial treatment for these disorders. We observed three patients with hereditary glomerulonephritis with plasma creatinine concentrations ranging from 1.7 to 2.0 mg/dL who were treated with angiotensin-converting enzyme inhibitors (ACEIs) for 3.5 to 6 years. Angiotensin-converting enzyme inhibitor therapy was accompanied by a decrease in the mean arterial pressure (MAP) from 115 +/- 10 mm Hg to 93 +/- 2 mm Hg (+/- SD), a decrease in the mean urinary protein/creatinine ratio from 2,910 +/- 1,720 mg/g to 391 +/- 355 mg/g, and stabilization of the decline of creatinine clearance with time in two of the three patients. Based on this apparent benefit of ACEIs in hereditary nephritis, we suggest that a prospective controlled trial of ACEIs should be undertaken among a large group of such patients. Pending the results of such a study, ACEIs should be considered for the treatment of patients with proteinuric and progressive hereditary nephritis.

L6 ANSWER 95 OF 166 MEDLINE on STN
ACCESSION NUMBER: 96217167 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8686202
TITLE: [A protein-restricted diet combined with ACE inhibitors does not improve insulin sensitivity in renal hypertension].
Dieta s obmedzenym privodom bielkovin v kombinacii s ACEI nezlepsuje inzulinovu senzitivitu pri nefrogennej hypertenzii.
AUTHOR: Spustova V; Stefikova K; Oksa A; Dzurik R
CORPORATE SOURCE: Klinika farmakoterapie Ustavu preventivnej a klinickej mediciny, Bratislava.
SOURCE: Vnitr ni lekar stvi, (1996 Mar) Vol. 42, No. 3, pp. 157-61.
Journal code: 0413602. ISSN: 0042-773X.
PUB. COUNTRY: Czech Republic
DOCUMENT TYPE: (CLINICAL TRIAL)
(CONTROLLED CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Slovak
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199608
ENTRY DATE: Entered STN: 28 Aug 1996
Last Updated on STN: 28 Aug 1996
Entered Medline: 21 Aug 1996

AB Hypertension is one of the most important accelerating factors for

progression of nephropathies. Its prevalence is about 35% in patients with nephropathies, even in minor or medium severe functional impairment. This is evidence that it is essential to select an optimal therapeutic regimen as soon as possible. A group of 38 patients (14 hypertensive patients) with a minor or medium severe functional impairment were included in a controlled trial. The patients were served a low-protein diet--0.6-0.7 g/kg/day and 2-10mg enalapril/day divided into two doses. The amount of enalapril depended on the blood pressure and enalapril was given also to normotensive patients. The investigation lasted 8 months. In the course of 8 months the authors did not reveal progression of the renal disease, as apparent from results of assessment of the creatinine level and clearance, assessment of uric acid and urea. The authors did not find deterioration of metabolic acidosis, nor of nephrogenic anaemia. Hypertensive patients had a tendency to deteriorating of insulin sensitivity while in normotensive patients a decline of triacylglycerols, VLDL and rise of HDL was recorded. The total cholesterol and LDL cholesterol level did not change. The authors conclude that the combination of a low-protein diet with ACEI in hypertensive and normotensive patients with mild to medium severe functional disorders inhibits the progression of nephropathies, but in hypertensive patients it does not prevent deterioration of insulin sensitivity.

L6 ANSWER 96 OF 166 MEDLINE on STN
ACCESSION NUMBER: 96116316 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8801325
TITLE: Reabsorption and metabolism of quinapril and quinaprilat in rat kidney: in vivo micropuncture studies.
AUTHOR: Smith D E; Kugler A R; Schnermann J B
CORPORATE SOURCE: College of Pharmacy, University of Michigan, Ann Arbor 48109-0504, USA.
CONTRACT NUMBER: R01 GM35498 (NIGMS)
SOURCE: Journal of pharmaceutical sciences, (1995 Oct) Vol. 84, No. 10, pp. 1147-50.
Journal code: 2985195R. ISSN: 0022-3549.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199609
ENTRY DATE: Entered STN: 15 Oct 1996
Last Updated on STN: 15 Oct 1996
Entered Medline: 30 Sep 1996

AB The tubular uptake and esterolysis of quinapril and quinaprilat were studied in male Sprague-Dawley rats using an in vivo micropuncture technique. [3H]Quinapril or [3H]quinaprilat was injected with [14C]inulin into either proximal or distal segments of the renal tubules, and urine was collected over 30 min. Urine and perfusate were assayed for [14C]-inulin using dual label spectrometry. [3H]Quinapril and [3H]quinaprilat concentrations were determined in urine and perfusate using a reversed-phase HPLC procedure with radiochemical detection, coupled to liquid scintillation spectrometry. These studies demonstrated that quinapril could access the esterase enzyme from tubular fluid and be metabolized to quinaprilat in both proximal and to a lesser extent distal segments of the kidney tubule. Quinapril, but not quinaprilat, was extensively reabsorbed. Its reabsorption along the proximal tubule and/or the loop of Henle could account for as much as 45-50% of the available dose of quinapril. Further, the urinary recovery of quinapril and quinaprilat (after dosing quinapril into proximal segments) was urine flow rate dependent.

L6 ANSWER 97 OF 166 MEDLINE on STN

ACCESSION NUMBER: 96097210 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7502416
TITLE: Effect of angiotensin-converting enzyme inhibition on nephropathy in patients with a remnant kidney.
AUTHOR: Novick A C; Schreiber M J Jr
CORPORATE SOURCE: Department of Urology, Cleveland Clinic Foundation, OH 44195, USA.
SOURCE: Urology, (1995 Dec) Vol. 46, No. 6, pp. 785-9.
Journal code: 0366151. ISSN: 0090-4295.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199601
ENTRY DATE: Entered STN: 17 Feb 1996
Last Updated on STN: 17 Feb 1996
Entered Medline: 17 Jan 1996

AB OBJECTIVES. This study was performed to evaluate the effect of angiotensin-converting enzyme inhibitor (ACEI) therapy and dietary protein restriction on nephropathy involving a remnant kidney. METHODS. Five patients with proteinuria > or = 5 years following partial removal of a solitary kidney were treated with a low-protein diet and an ACEI agent. Four patients had biopsy-proven focal segmental glomerulosclerosis. The daily urinary protein excretion ranged from 1240 to 10,032 mg. The serum creatinine levels ranged from 1.2 to 3.1 mg/dL. RESULTS. The post-treatment follow-up interval ranged from 18 to 30 months. The treatment regimen was well tolerated in all patients. Four patients experienced a reduction in the urinary protein level while maintaining stable overall renal function. In 1 patient, the urinary protein level increased and renal function gradually deteriorated following ACEI therapy. CONCLUSIONS. These preliminary data suggest that ACEI therapy and a low-protein diet may mitigate nephropathy associated with a remnant kidney.

L6 ANSWER 98 OF 166 MEDLINE on STN
ACCESSION NUMBER: 96062374 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7473177
TITLE: Moexipril, a new angiotensin-converting enzyme (ACE) inhibitor: pharmacological characterization and comparison with enalapril.
AUTHOR: Edling O; Bao G; Feelisch M; Unger T; Gohlke P
CORPORATE SOURCE: Department of Pharmacology, University of Kiel, Germany.
SOURCE: The Journal of pharmacology and experimental therapeutics, (1995 Nov) Vol. 275, No. 2, pp. 854-63.
Journal code: 0376362. ISSN: 0022-3565.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199512
ENTRY DATE: Entered STN: 24 Jan 1996
Last Updated on STN: 24 Jan 1996
Entered Medline: 19 Dec 1995

AB The pharmacodynamic profile of the new angiotensin-converting enzyme (ACE) inhibitor moexipril and its active diacid, moexiprilat, was studied in vitro and in vivo. In vitro, moexiprilat exhibited a higher inhibitory potency than enalaprilat against both plasma ACE and purified ACE from rabbit lung. Upon oral administration of moexipril (10 mg/kg/day) to spontaneously hypertensive rats, plasma angiotensin II concentration decreased to undetectable levels, plasma ACE activity was inhibited by 98% and plasma angiotensin I concentration increased 8.6-fold 1 h after dosing. At 24 h, plasma angiotensin I and angiotensin II concentrations had returned to pretreatment levels, whereas plasma ACE

activity was still inhibited by 56%. Four-week oral administration of moexipril (0.1-30 mg/kg/day) to spontaneously hypertensive rats lowered blood pressure and differentially inhibited ACE activity in plasma, lung, aorta, heart and kidney in a dose-dependent fashion. Equidose treatment (10 mg/kg/day) with moexipril and enalapril over 4 weeks led to comparable decreases in blood pressure, inhibition of plasma ACE and reduction of plasma angiotensinogen and to a similar attenuation of the pressor responses to angiotensin I and potentiation of the depressor responses to bradykinin. In contrast, ACE inhibition in aorta, heart and lung was significantly greater with moexipril than with enalapril, whereas in the kidney both drugs inhibited ACE activity to a similar extent. In summary, moexipril is an orally active ACE inhibitor that is comparable to enalapril in potency and duration of antihypertensive activity. The results of the present study demonstrate that 1) the antihypertensive potency of a given ACE inhibitor cannot be predicted from its in vitro characteristics and 2) the degree of blood pressure reduction does not correlate with tissue ACE inhibition.

L6 ANSWER 99 OF 166 MEDLINE on STN
ACCESSION NUMBER: 96037039 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7496563
TITLE: Effect of enalapril on erythrocytosis in hypertensive patients with renal disease.
AUTHOR: Shand B I; Bailey R R; Lynn K L; Robson R A
CORPORATE SOURCE: Department of Nephrology, Christchurch Hospital, New Zealand.
SOURCE: Blood pressure, (1995 Jul) Vol. 4, No. 4, pp. 238-40. Journal code: 9301454. ISSN: 0803-7051.
PUB. COUNTRY: Norway
DOCUMENT TYPE: (CLINICAL TRIAL) Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199601
ENTRY DATE: Entered STN: 17 Feb 1996
Last Updated on STN: 17 Feb 1996
Entered Medline: 18 Jan 1996

AB Treatment of hypertension with an angiotensin converting enzyme inhibitor (ACEI) may be associated with a decrease in haemoglobin concentration especially in patients with renal insufficiency. This open study in 19 patients with a variety of renal diseases with complicating hypertension investigated the effects of the ACEI, enalapril, on haemoglobin and plasma erythropoietin (EPO) concentrations. Blood samples were obtained at baseline and 2, 60 and 120 days after starting treatment with enalapril. By day 60 there was a significant decrease in mean haemoglobin concentration (mean decrease 7.4 g/l) that was sustained until day 120. Apart from a small, but significant, reduction by day 2, mean plasma EPO concentration remained constant throughout the study. The magnitude of the decrease in haemoglobin concentration was, however, significantly correlated with the baseline plasma creatinine concentration and creatinine clearance. These results suggested that the degree of renal insufficiency was important in determining the haematological response to ACE inhibition. While the mechanism of these changes remains unclear, our findings suggest that inhibition of the renin-angiotensin system, rather than decreasing EPO production, may reduce the erythropoietic activity of the hormone.

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L6 ANSWER 80 OF 166 MEDLINE on STN
ACCESSION NUMBER: 97173626 MEDLINE

DOCUMENT NUMBER: PubMed ID: 9021525
TITLE: Effects of treatment with angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor antagonist (AIIRA) on renal function and glomerular injury in subtotal nephrectomized rats.
AUTHOR: Yamamoto M; Fukui M; Shou I; Wang L N; Sekizuka K; Suzuki S; Shirato I; Tomino Y
CORPORATE SOURCE: Department of Medicine, Juntendo University School of Medicine, Tokyo, Japan.
SOURCE: Journal of clinical laboratory analysis, (1997) Vol. 11, No. 1, pp. 53-62.
Journal code: 8801384. ISSN: 0887-8013.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199704
ENTRY DATE: Entered STN: 7 May 1997
Last Updated on STN: 7 May 1997
Entered Medline: 25 Apr 1997

AB The aim of this study was to determine if treatment with angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor antagonists (AIIRA) might decrease urinary albumin excretion and prevent glomerular enlargement and glomerulosclerosis in subtotal (5/6) nephrectomized rats. Morphometric image analysis of glomeruli was also performed in the subtotal nephrectomized rats. The nephrectomized rats were treated with ACEI (enalapril 100 mg/l), AIIRA (L-158,809 10 mg/l) or TRX (reserpine 5 mg/ l, hydralazine 80 mg/l, and hydrochlorothiazide 25 mg/l) and euthanized at 16 weeks after renal ablation. Treatments were started at 2 weeks (early treatment: Group I) or 8 weeks (later treatment: Group II) after the ablation. ACEI and AIIRA treatments were equally and significantly effective in limiting albuminuria and progression of glomerular sclerosis. TRX was also as effective in decreasing urinary albumin excretion and preserving the renal function as ACEI or AIIRA in Group I. The improvement of albuminuria, glomerular enlargement and sclerosis after these treatments in Group II was significantly less than that in Group I. It appears that the early treatment with angiotensin converting enzyme inhibitor, angiotensin II receptor antagonist or reserpine, hydralazine and hydrochlorothiazide (TRX) may prevent glomerular injury in human patients with renal hypertension.

L6 ANSWER 81 OF 166 MEDLINE on STN
ACCESSION NUMBER: 97163955 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9010710
TITLE: Lack of a pharmacokinetic interaction between moexipril and hydrochlorothiazide.
AUTHOR: Hutt V; Michaelis K; Verbesselt R; De Schepper P J; Salomon P; Bonn R; Cawello W; Angehrn J C
CORPORATE SOURCE: LAB Gesellschaft fur Pharmakologische Untersuchungen mbH and Co, Neu-Ulm, Germany.
SOURCE: European journal of clinical pharmacology, (1996) Vol. 51, No. 3-4, pp. 339-44.
Journal code: 1256165. ISSN: 0031-6970.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199704
ENTRY DATE: Entered STN: 14 Apr 1997
Last Updated on STN: 14 Apr 1997

Entered Medline: 1 Apr 1997

AB OBJECTIVE: To investigate the potential for pharmacokinetic interactions between moexipril, a new converting enzyme inhibitor, and hydrochlorothiazide after single dose administration. METHODS: 12 healthy male volunteers were studied by an open, randomised, three-way cross-over design, in which single doses of moexipril, hydrochlorothiazide and the two drugs together were administered. Blood and urine were collected up to 48 hours for measurement of the concentrations of moexipril and its metabolite moexiprilat. In addition, the urine samples were analysed for hydrochlorothiazide. RESULTS: For the area under the plasma concentration-time curve calculated from time 0 to a concentration greater than zero, AUC(0-t), the study showed a mean value of moexipril 437 ng.ml-1.h-1 following administration of moexipril alone and 416 ng.ml-1.h-1 following moexipril concomitantly with hydrochlorothiazide. The corresponding values for the metabolite moexiprilat were 203 and 215 ng.ml-1.h-1, respectively. The Cmax of moexipril and the metabolite (data of the metabolite in parenthesis) were 245.4 (70.8) ng.ml-1 after administration of moexipril alone and 241.0 (69.2) ng.ml-1 after coadministration of hydrochlorothiazide. The mean total renal excretion (TUE) of hydrochlorothiazide was 15.2 mg when administered alone and 15.1 mg when given together with moexipril. The corresponding mean TUE-values for moexiprilat were 334 (1200) and 453 (1460) micrograms. CONCLUSIONS: The coadministration of moexipril with hydrochlorothiazide had no demonstrable effect on the measured pharmacokinetic parameters of moexipril, its active metabolite moexiprilat or hydrochlorothiazide.

L6 ANSWER 82 OF 166 MEDLINE on STN

ACCESSION NUMBER: 97148905 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8995730
TITLE: Modulation of plasminogen activator inhibitor-1 in vivo: a new mechanism for the anti-fibrotic effect of renin-angiotensin inhibition.
AUTHOR: Oikawa T; Freeman M; Lo W; Vaughan D E; Fogo A
CORPORATE SOURCE: Department of Pathology, Vanderbilt University Medical Center, Nashville, Tennessee, USA.
CONTRACT NUMBER: DK 44757 (NIDDK)
R01 HL 51387 (NHLBI)
SOURCE: Kidney international, (1997 Jan) Vol. 51, No. 1, pp. 164-72.
Journal code: 0323470. ISSN: 0085-2538.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199703
ENTRY DATE: Entered STN: 14 Apr 1997
Last Updated on STN: 3 Mar 2000
Entered Medline: 31 Mar 1997

AB We examined the potential of in vivo linkage of plasminogen activator inhibitor-1 (PAI-1) and angiotensin II (Ang II) in the setting of endothelial injury and sclerosis following radiation injury in the rat. PAI-1 is a major physiological inhibitor of the plasminogen activator (PA)/plasmin system, a key regulator of fibrinolysis and extracellular matrix (ECM) turnover. PAI-1 mRNA expression in the kidney was markedly increased (9-fold) at 12 weeks after irradiation ($P < 1.001$ vs. normal control). In situ hybridization revealed significant association of PAI-1 expression with sites of glomerular injury (signal intensity in injured vs. intact glomeruli, $P < 0.001$). Angiotensin converting enzyme inhibitors (ACEI, captopril or enalapril) or angiotensin II receptor antagonist (AIIRA, L158,809) markedly reduced glomerular lesions (thrombosis, mesangiolysis, and sclerosis; sclerosis index, 0 to 4+ scale, 0.49 +/- 0.20 in untreated vs. 0.05 +/- 0.02, 0.02

+/- 0.01, 0.04 +/- 0.02 in captopril, enalapril and AIIRA, respectively, all P < 0.01 vs untreated). Further, ACEI and AIIRA markedly attenuated increased PAI-1 mRNA expression in the irradiated kidney (36, 19 and 20% expression, respectively, for captopril, enalapril and AIIRA, compared to untreated irradiated kidney, P < 0.05, < 0.01, < 0.01). This effect was selective in that neither tissue-type nor urokinase-type PA mRNA expression was affected by these interventions. Thus, we speculate that inhibition of the renin-angiotensin system may ameliorate injury following radiation by accelerating fibrinolysis and ECM degradation, at least in part, via suppression of PAI-1 expression. In summary, inhibition of Ang II, in addition to its known effects on vascular sclerosis, may also by its novel effect to inhibit PAI-1, lessen fibrosis following endothelial/thrombotic injury.

L6 ANSWER 83 OF 166 MEDLINE on STN
ACCESSION NUMBER: 97140435 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8986916
TITLE: Antihypertensive effects and arterial haemodynamic alterations during angiotensin converting enzyme inhibition.
AUTHOR: London G M; Pannier B; Vicaut E; Guerin A P; Marchais S J; Safar M E; Cuche J L
CORPORATE SOURCE: Centre Hospitalier F.H. Manhes, Fleury-Merogis, France.
SOURCE: Journal of hypertension, (1996 Sep) Vol. 14, No. 9, pp. 1139-46.
Journal code: 8306882. ISSN: 0263-6352.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: (CLINICAL TRIAL)
(CONTROLLED CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199703
ENTRY DATE: Entered STN: 27 Mar 1997
Last Updated on STN: 29 Jan 1999
Entered Medline: 20 Mar 1997

AB OBJECTIVE: To assess the respective roles of the anti-hypertensive and blood pressure-independent effects of angiotensin converting enzyme (ACE) inhibition in the changed arterial haemodynamics observed in hypertensive patients with end-stage renal disease (ESRD) treated by haemodialysis. DESIGN AND METHODS: Twelve hypertensive patients with ESRD were included in a double-blind, cross-over study comparing a single 20 mg dose of the ACE inhibitor quinapril versus placebo. Two study periods each of 172 h duration were separated by a 2-week placebo period. Repeated measurements of the following parameters were performed: brachial artery systolic blood pressure (SBP); diastolic blood pressure and mean blood pressure (using a mercury sphygmomanometer); carotid artery SBP and pulse pressure (by applanation tonometry); aortic stiffness (by pulse wave velocity); and the effect of arterial wave reflections in the common carotid artery (the augmentation index, by applanation tonometry). A radioimmunoassay was used to determine plasma angiotensin II levels. Quinaprilat pharmacokinetics were studied using a specific assay. Two-way (time-treatment) analysis of variance for repeated measures, analysis of covariance for two within-factors and a covariate changing with the level of the factor time (pressures measured at each time) and baseline values of the studied parameter as a second covariate were used for statistical analysis. RESULTS: Quinapril treatment induced a long-lasting decrease in arterial wave reflections, which was still observable 172 h after quinapril administration and still present after removing the effect of the decrease in blood pressure. The effect on wave reflections was associated with a more pronounced and sustained decrease in carotid SBP and pulse pressure than that in brachial SBP and pulse pressure. Quinapril administration also induced a long-lasting decrease

in aortic pulse wave velocity, but this effect was entirely dependent on parallel changes in blood pressure. Arterial haemodynamic changes were not related to plasma angiotensin II or quinaprilat levels. CONCLUSIONS: The results of this controlled study indicate that, in ESRD patients, ACE inhibition results in a long-lasting, blood pressure-independent decrease in arterial wave reflections. The consequence of this was a decrease in pulsatile pressure load in the central arteries with increased aortic distensibility. The increased aortic distensibility resulted from the decrease in blood pressure. The observed arterial haemodynamic alterations suggest that ACE inhibition induced alterations in arterial wave reflections in the distal parts of the arterial tree.

L6 ANSWER 84 OF 166 MEDLINE on STN
ACCESSION NUMBER: 97123137 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8968386
TITLE: Single-domain angiotensin I converting enzyme (kininase II): characterization and properties.
AUTHOR: Deddish P A; Wang L X; Jackman H L; Michel B; Wang J; Skidgel R A; Erdos E G
CORPORATE SOURCE: Department of Pharmacology, University of Illinois College of Medicine, Chicago, USA.
CONTRACT NUMBER: HL36473 (NHLBI)
SOURCE: The Journal of pharmacology and experimental therapeutics, (1996 Dec) Vol. 279, No. 3, pp. 1582-9.
Journal code: 0376362. ISSN: 0022-3565.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199701
ENTRY DATE: Entered STN: 19 Feb 1997
Last Updated on STN: 19 Feb 1997
Entered Medline: 23 Jan 1997

AB Somatic angiotensin I converting enzyme (ACE; kininase II) has two active sites, in two (N and C) domains. We studied the active centers with separate N-domain ACE (N-ACE), testicular C-domain ACE (germinal ACE) and, as control, renal somatic ACE. Germinal ACE cleaved the nonapeptide bradykinin about two times faster than N-ACE in 20 mM Cl-. Bradykinin1-7 was hydrolyzed further to bradykinin1-5 by N-ACE four times faster in the absence of Cl-, but at 300 mM Cl- the C-domain hydrolyzed it twice as fast. The hematopoietic system regulatory peptide acetyl-Ser-Asp-Lys-Pro was split to two dipeptides by N-ACE, depending on the chloride concentration, 8 to 24 times faster than by germinal ACE; at 100 mM Cl-, the Kcat with N-ACE was eight times higher. One millimolar 1-fluoro-2,4-dinitrobenzene inhibited germinal ACE 96% but it inhibited N-ACE by only 31%. [3H]Ramiprilat was displaced by other unlabeled ACE inhibitors to establish their relative affinities. Captopril had the lowest IC50 (0.5 nM) with N-ACE and the highest IC50 (8.3 nM) with the germinal ACE. The IC50 values of ramiprilat and quinaprilat were about the same with both active sites. The association and dissociation constants of [3H]ramiprilat indicated faster association with and faster dissociation from N-ACE than from germinal ACE. After exposure to alkali or moderate heat, somatic ACE was cleaved by plasmin and kallikrein, releasing N-ACE and apparently inactivating the C-domain. These studies affirm the differences in the activity, stability and inhibition of the two active sites of ACE.

L6 ANSWER 85 OF 166 MEDLINE on STN
ACCESSION NUMBER: 97026795 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8872973
TITLE: Mechanism of angiotensin converting enzyme inhibitor-related anemia in renal transplant recipients.

AUTHOR: Gossmann J; Thurmann P; Bachmann T; Weller S; Kachel H G; Schoeppe W; Scheuermann E H
CORPORATE SOURCE: Abt. f. Nephrologie, Johann Wolfgang Goethe-Universitat, Frankfurt/Main, Germany.
SOURCE: Kidney international, (1996 Sep) Vol. 50, No. 3, pp. 973-8. Journal code: 0323470. ISSN: 0085-2538.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL) Journal; Article; (JOURNAL ARTICLE) (RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199701
ENTRY DATE: Entered STN: 28 Jan 1997
Last Updated on STN: 28 Jan 1997
Entered Medline: 6 Jan 1997

AB To delineate the pathogenesis of the reduction in hemoglobin occurring in renal transplant patients treated with angiotensin converting enzyme inhibitors (ACEI) and azathioprine (AZA) a controlled, prospective trial of ACEI withdrawal was conducted. The ACEI was replaced by nifedipine or clonidine in 15 kidney transplant patients immunosuppressed with AZA and prednisone (enalapril in 14 and captopril in 1). Before and during 10 to 12 weeks after withdrawal of the ACEI, AZA metabolites, renal function parameters and hematological parameters including erythropoietin and reticulocytes were evaluated. Enalaprilat levels were measured and compared with 15 similar patients matched for transplant function and enalapril dosage immunosuppressed with cyclosporine and prednisone. AZA metabolites did not differ significantly in the presence or absence of the ACEI. Enalaprilat levels also showed no significant difference between the two patient groups treated with AZA or cyclosporine. Hematocrit and hemoglobin increased significantly from 37.5 +/- 6.4 to 39.7 +/- 3.6% (mean +/- SD, P = 0.02) and 12.8 +/- 2.2 to 13.5 +/- 1.2 g/dl, P = 0.04, respectively, 10 to 12 weeks after ACEI treatment had been discontinued. Simultaneously numbers of reticulocytes and erythropoietin concentrations rose significantly after 2, 4 and 10 weeks, with a peak at two weeks (from 14.1 +/- 3.8 to 20.6 +/- 8.0/1000, P < 0.05 and from 14.3 +/- 12.4 to 29.3 +/- 54.5 mU/ml, P < 0.05, respectively). In conclusion, ACEI-related anemia in renal transplant recipients seems to be due to the erythropoietin-lowering effect of this group of drugs. A pharmacokinetic interaction between AZA and enalapril is not likely since plasma enalaprilat levels were independent of the immunosuppressive regimen and AZA metabolite levels were unchanged in the presence and absence of the ACEI. Several mechanisms by which angiotensin converting enzyme blockade may cause a decrease in circulating erythropoietin are discussed.

L6 ANSWER 86 OF 166 MEDLINE on STN
ACCESSION NUMBER: 97022643 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8869003
TITLE: Does combined therapy of Ca-channel blocker and angiotensin converting enzyme inhibitor exceed monotherapy in renal protection against hypertensive injury in rats?.
AUTHOR: Kanno Y; Okada H; Suzuki H; Ikenaga H; Ishii N; Itoh H; Saruta T
CORPORATE SOURCE: Department of Internal Medicine, Keio University, Tokyo, Japan.
SOURCE: Clinical and experimental hypertension (New York, N.Y. : 1993), (1996 Feb) Vol. 18, No. 2, pp. 243-56. Journal code: 9305929. ISSN: 1064-1963.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 199701
ENTRY DATE: Entered STN: 28 Jan 1997
Last Updated on STN: 28 Jan 1997
Entered Medline: 3 Jan 1997

AB Either calcium channel blocker (CCB) or angiotensin converting enzyme inhibitor (ACEi) is used as an antihypertensive agent, and we are recommended to use them in combination to refractory hypertension with evidence dependent on clinical observations. We examined the renal protective effect of the combined therapy with calcium channel blocker (amlodipine) and angiotensin converting enzyme inhibitor (enalapril) against hypertensive renal injury in 5/6 nephrectomized spontaneously hypertensive rats (SHRs) with salt loading, comparing with monotherapy of each drug. Forty males SHRs with 5/6 nephrectomy and salt loading were divided to five groups: group 1 as control (n = 8), group 2 received 0.2 mg/kg/day of amlodipine (n = 8), group 3 received 0.2 mg/kg/day of enalapril (n = 8), group 4 (n = 8) and group 5 (n = 8) that were treated with 0.1 mg/kg/day and 0.2 mg/kg/day of each drug in combination respectively. Either amlodipine or enalapril had remarkable effects on reducing the increases in blood pressure and urinary protein excretion. In histopathological examination, it also suppressed renal injury significantly. Additional significant effect of combined therapy was not observed in blood pressure and urinary protein. There were not remarkable, additional effects of the combination of CCB and ACEi on protecting the remnant kidney in 5/6 nephrectomized SHRs fed a high-salt diet, possibly because sodium retention was not alleviated by the combination.

L6 ANSWER 87 OF 166 MEDLINE on STN
ACCESSION NUMBER: 96431115 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8834197
TITLE: Disposition of quinapril and quinaprilat in the isolated perfused rat kidney.
AUTHOR: Kugler A R; Olson S C; Smith D E
CORPORATE SOURCE: Department of Pharmacokinetics and Drug Metabolism, Parke-Davis Pharmaceutical Research, Ann Arbor, Michigan 48106-1047, USA.
CONTRACT NUMBER: GM35498 (NIGMS)
SOURCE: Journal of pharmacokinetics and biopharmaceutics, (1995 Jun) Vol. 23, No. 3, pp. 287-305.
Journal code: 0357115. ISSN: 0090-466X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199611
ENTRY DATE: Entered STN: 19 Dec 1996
Last Updated on STN: 19 Dec 1996
Entered Medline: 27 Nov 1996

AB An isolated perfused rat kidney model was used to probe the renal disposition of quinapril and quinaprilat after separate administration of each drug species. Control studies were performed with drug-free perfusate (n = 8) and perfusate containing quinapril (n = 9) or quinaprilat (n = 7) at initial drug concentrations of 1000 ng/ml (including corresponding tracer levels of tritiated drug). Physiologic parameters were within the normal range of values for this technique and were stable for the duration of each experiment. Quinapril and quinaprilat concentrations were determined in perfusate, urine, and perfusate ultrafiltrate using a specific and sensitive reversed-phase HPLC procedure with radiochemical detection, coupled to liquid scintillation spectrometry. Perfusate protein binding was determined using an ultrafiltration method at 37 degrees C. The total renal clearance of quinapril (CLr) was calculated as Dose/AUC(0-infinity), and is represented by the sum of its

urinary and metabolic clearances. The urinary clearances (CLe) of quinapril and quinaprilat were calculated as urinary excretion rate divided by midpoint perfusate concentration for each respective species. Of the total renal clearance for quinapril (CLr = 4.49 ml/min), less than 0.1% was cleared as unchanged drug (CLe = 0.004 ml/min); over 99% of the drug was cleared as quinaprilat formed in the kidney. The clearance ratio of quinapril [CR = CLr/(fu.GFR)] was 41.0, a value representing extensive tubular secretion into the renal cells. Following quinaprilat administration, the clearance ratio of metabolite [CR = CLe/(fu.GFR)] was 3.85, indicating a net secretion process for renal elimination.

L6 ANSWER 88 OF 166 MEDLINE on STN
ACCESSION NUMBER: 96345859 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8767069
TITLE: [Effect of enalapril on microalbuminuria and lipid profile of normotensive type I diabetes mellitus patients].
Influencia de enalapril sobre la microalbuminuria y el perfil lipidico en pacientes con diabetes mellitus tipo I normotensos.
AUTHOR: Hernandez Mijares A; Barbera Comes G; Lluch Verdu I; Morillas Arino C; Real Collado J; Lorente Calvo R; Gonzalez Bayo E; Carmena Rodriguez R
CORPORATE SOURCE: Servicio de Endocrinologia, Hospital Dr. Peset, Universidad de Valencia.
SOURCE: Revista clinica espanola, (1996 Jun) Vol. 196, No. 6, pp. 354-8.
Journal code: 8608576. ISSN: 0014-2565.
PUB. COUNTRY: Spain
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Spanish
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 28 Jan 1997
Last Updated on STN: 28 Jan 1997
Entered Medline: 19 Dec 1996

AB A longitudinal study for six months was conducted to demonstrate the influence of enalapril therapy on microalbuminuria in a group of patients with IDDM without arterial hypertension. An evaluation was also considered of its possible activity on other biochemical parameters, particularly plasma lipid levels. Thirty-four patients with IDDM were selected, with a mean age of 26.1 +/- 7.2 years and a mean clinical course of 11.8 +/- 5.6 years. Arterial blood pressure (ABP) was confirmed lower than 140/85 mmHg in all cases. Patients were administered 5 mg/day of enalapril and if a decrease in microalbuminuria higher than 25% was not achieved at the end of the first month of therapy, the dose was doubled (10 mg/day). No significant differences were found in ABP and in HbA1c throughout the study period. Albumin excretion in the initial period was 125.1 +/- 79.28 mg/24 h, at one month in the follow-up 47.6 +/- 44.1 mg/24 h, at three months 23.8 +/- 18.1 mg/24 h, and at the end of the 6th month 15.33 +/- 6.9 mg/24 h, all differences being significant. Renal function parameters and Na+ and K+ measurements remained unchanged for the follow-up period. No significant changes were detected for lipid and lipoprotein values for the length of the study. We conclude that therapy with enalapril in insulin-dependent diabetic patients without hypertension has an important effect on microalbuminuria during the first month of therapy; a stabilization in the normal range was reached in the third and sixth months of follow-up. No changes in arterial blood pressure nor in renal function were observed. Plasma lipid values were in the normal range throughout the study. Therefore, treatment for microalbuminuria with the ACEI assayed was efficient, in absence of arterial hypertension and irrespective of the

metabolic control obtained. Future long-term studies are needed to evaluate the possible delay in the emergence of renal insufficiency.

L6 ANSWER 89 OF 166 MEDLINE on STN
ACCESSION NUMBER: 96336614 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8743512
TITLE: Therapeutic advantages of angiotensin converting enzyme inhibitors in chronic renal disease.
AUTHOR: Omata K; Kanazawa M; Sato T; Abe F; Saito T; Abe K
CORPORATE SOURCE: Second Department of Internal Medicine, Tohoku University School of Medicine, Sendai, Japan.
SOURCE: Kidney international. Supplement, (1996 Jun) Vol. 55, pp. S57-62.
Journal code: 7508622. ISSN: 0098-6577.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199611
ENTRY DATE: Entered STN: 19 Dec 1996
Last Updated on STN: 19 Dec 1996
Entered Medline: 20 Nov 1996

AB More than other drugs, angiotension converting enzyme (ACE) inhibitors have been shown to provide better control of glomerular hypertension and improved preservation of renal function. Long-term treatment with captopril slows the progression of renal impairment in diabetic nephropathy; however, the data are inconclusive for non-diabetic nephropathies. ACE inhibitors such as captopril, enalapril, alacepril delapril cilazapril, and lisinopril were equally effective in reducing blood pressure in multicenter clinical trials focusing on renal hypertension in Japan. We studied the influence of ambulatory blood pressure (ABP) and the effects of hypertension therapy in 104 patients with chronic renal glomerulonephritis as diagnosed by renal biopsy. Patients were subdivided into hypertensive, normotensive and hypotensive groups according to ABP and ages. Hypotensive subjects showed an improvement, while normotensive subjects showed a slower rate of progression of renal function loss than hypertensive patients. This suggests that the adequate ABP levels were 100 to 125/55 to 75 in those who were less than 40 years old, 100 to 135/60 to 80 mm Hg in patients aged 40 to 60, and 105 to 140/60 to 85 mm Hg in those over 60 years old. The renal protective effects of calcium antagonists and ACE inhibitors were associated with a reduction in blood pressure, but not with the hypotensive action.

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L6 ANSWER 70 OF 166 MEDLINE on STN
ACCESSION NUMBER: 1998139205 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9527398
TITLE: Effects of combination therapy with enalapril and losartan on the rate of progression of renal injury in rats with 5/6 renal mass ablation.
AUTHOR: Ots M; Mackenzie H S; Troy J L; Rennke H G; Brenner B M
CORPORATE SOURCE: Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts 02115, USA.
SOURCE: Journal of the American Society of Nephrology : JASN, (1998 Feb) Vol. 9, No. 2, pp. 224-30.
Journal code: 9013836. ISSN: 1046-6673.
PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199804
ENTRY DATE: Entered STN: 10 Apr 1998
Last Updated on STN: 10 Apr 1998
Entered Medline: 2 Apr 1998

AB Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor antagonists (AT1RA) slow the rate of progression of experimental renal disease. Although the end result of both classes of drugs is to block the renin-angiotensin system (RAS), ACEI and AT1RA act at different sites in the RAS cascade. The aim of this study was to compare the effects of an ACEI (enalapril) and AT1RA (losartan), alone or in combination, in slowing the progression of experimental renal disease in a model of reduced renal mass. Two weeks after 5/6 renal ablation, rats were divided into five groups matched for body weight, systolic BP (SBP), and urinary protein excretion rate (UprotV). The effects on SBP and UprotV of treatment with 25 and 40 mg/L enalapril (groups I and II; both n = 7), 180 mg/L losartan (group III, n = 8), or a combination of enalapril (25 mg/L) + losartan (180 mg/L) (group IV, n = 9) versus vehicle (group V, n = 9) were studied for 12 wk. Remnant kidneys were then assessed histologically for evidence of focal and segmental glomerulosclerosis and hyalinosis (FSGS), and interstitial fibrosis. There were no significant differences (NSD) in body weight among the groups at any time. Combination therapy reduced SBP (122 +/- 8 mmHg) significantly at 12 wk to levels similar to losartan (127 +/- 3 mmHg) or enalapril (40 mg/L) alone (124 +/- 5 mmHg) ($P < 0.05$ versus vehicle controls). With equivalent antihypertensive effects, no differences in frequency of FSGS were discerned among the treatment groups (groups II through IV; $F = 1.7$, NSD). Tubulointerstitial injury scores followed a similar pattern. BP was highly correlated with the extent of FSGS, both among individual rats ($r = 0.68$, $P = 0.05$) and the group means ($r = 0.99$, $P = 0.001$). We conclude that the renoprotective effects of enalapril, losartan, or combination therapy are similar in this model over the 12 wk of the study, and are closely related to the magnitude of their antihypertensive effects.

L6 ANSWER 71 OF 166 MEDLINE on STN
ACCESSION NUMBER: 1998071333 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9407442
TITLE: Effects of candesartan cilexetil (TCV-116) and enalapril in 5/6 nephrectomized rats.
AUTHOR: Noda M; Fukuda R; Matsuo T; Ohta M; Nagano H; Imura Y; Nishikawa K; Shibouta Y
CORPORATE SOURCE: Pharmaceutical Research Laboratories II, Takeda Chemical Industries Ltd., Osaka, Japan.. Noda_Masakuni@takeda.co.jp
SOURCE: Kidney international. Supplement, (1997 Dec) Vol. 63, pp. S136-9.
Journal code: 7508622. ISSN: 0098-6577.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199802
ENTRY DATE: Entered STN: 17 Feb 1998
Last Updated on STN: 13 Mar 2003
Entered Medline: 5 Feb 1998

AB The renal protective properties of candesartan cilexetil (TCV-116), an angiotensin II type 1 receptor antagonist (AT1A), and enalapril, an angiotensin I converting enzyme inhibitor (ACEI), were investigated in 5/6 nephrectomized (NX) rats. Candesartan cilexetil (1 mg/kg/day) and enalapril (10 mg/kg/day)

were administered orally to 5/6 NX rats for four weeks (during the early phase of disease development) or 16 weeks (through the late phase). In vehicle-treated rats, proteinuria, glomerulosclerosis, interstitial mononuclear cell (MNC) infiltration and interstitial fibrosis developed. Moreover, immunohistological studies showed enhanced expression of transforming growth factor-beta 1 (TGF-beta 1) in the injured glomeruli. Both drugs inhibited these adverse changes in the early phase. In the late phase, the progressive proteinuria, interstitial MNC infiltration were attenuated by both drugs. However, candesartan cilexetil significantly inhibited the progression of glomerulosclerosis, the expression of TGF-beta 1 and the interstitial fibrosis, while enalapril did not. Candesartan cilexetil and enalapril showed comparable hypotensive effects after the 16-week administration. These results indicate that candesartan cilexetil shows a more potent protective effect than enalapril against the progression of renal injury in the late phase. Thus, an AT1A might be more useful than an ACEI for the treatment of patients with chronic renal failure.

L6 ANSWER 72 OF 166 MEDLINE on STN
ACCESSION NUMBER: 1998071306 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9407415
TITLE: Angiotensin converting enzyme insertion/deletion polymorphism and short-term renal response to ACE inhibition: role of sodium status.
AUTHOR: van der Kleij F G; Schmidt A; Navis G J; Haas M; Yilmaz N; de Jong P E; Mayer G; de Zeeuw D
CORPORATE SOURCE: Department of Internal Medicine, State University Groningen, The Netherlands.
SOURCE: Kidney international. Supplement, (1997 Dec) Vol. 63, pp. S23-6.
Journal code: 7508622. ISSN: 0098-6577.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199802
ENTRY DATE: Entered STN: 17 Feb 1998
Last Updated on STN: 17 Feb 1998
Entered Medline: 5 Feb 1998

AB Angiotensin converting enzyme (ACEi) inhibition retards renal function loss, but the therapeutic benefit varies between individuals. Renoprotection is poor in patients with the ACE DD genotype. ACE genotype is reported to affect short-term antiproteinuric response to ACEi, a predictor of long-term renoprotection, in some studies but not in others. Short-term responses to ACEi are enhanced by stimulating the renin-angiotensin system, that is, sodium restriction. We hypothesized that the ACE genotype influences sodium dependency of the response to ACEi. Therefore, we performed a cross sectional analysis of short-term responses to ACEi (enalapril or lisinopril) in 88 patients with stable non-diabetic proteinuria (> 1.0 g/day) and variable sodium intake. ACE genotype distribution was: DD, N = 25; ID, N = 40; II, N = 23. Baseline proteinuria (5.9 +/- 0.7; 5.8 +/- 0.07; 4.8 +/- 0.8 g/day, respectively) and mean arterial pressure (108 +/- 3; 106 +/- 2; 107 +/- 2 mm Hg, respectively) were similar for the three genotypes. ACEi similarly reduced proteinuria (-49 +/- 5; -55 +/- 4, -48 +/- 6%, respectively) and blood pressure (-12 +/- 3; -14 +/- 1 and -12 +/- 2%, respectively) in the three groups. Interestingly, the responses to ACEi of proteinuria ($r = 0.42$, $P < 0.05$) and blood pressure ($r = 0.41$, $P < 0.05$) correlated with urinary sodium excretion in DD genotype but not in the ID ($r = 0.05$ and 0.17, resp) or II genotype ($r = 0.09$ and 0.08, respectively). Thus, in the DD group, individuals with a high sodium excretion had a less effective response to ACEi. We

conclude that differences in sodium status could account for disparities between studies on the relationship between ACE genotype and response to ACEi, and that sodium restriction might be a strategy to circumvent treatment resistance in the DD genotype.

L6 ANSWER 73 OF 166 MEDLINE on STN
ACCESSION NUMBER: 1998069084 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9406010
TITLE: Dietary protein restriction in combination with angiotensin converting enzyme inhibitor improves insulin resistance in patients with chronic renal disease.
AUTHOR: Stefikova K; Spustova V; Gazdikova K; Krivosikova Z; Dzurik R
CORPORATE SOURCE: Institute of Preventive and Clinical Medicine, Bratislava, Slovakia.
SOURCE: International urology and nephrology, (1997) Vol. 29, No. 4, pp. 497-507.
Journal code: 0262521. ISSN: 0301-1623.
PUB. COUNTRY: Hungary
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199801
ENTRY DATE: Entered STN: 17 Feb 1998
Last Updated on STN: 17 Feb 1998
Entered Medline: 30 Jan 1998

AB Insulin resistance (IR) and secondary hyperinsulinaemia are major risk factors of atherosclerosis and probably also of related glomerulosclerosis. Angiotensin converting enzyme inhibitors (ACEI), while improving IR in essential hypertension, do not improve it in patients with chronic renal disease. Thus, the combination of ACEI and low protein diet was evaluated. Thirty-eight patients with various kidney diseases and mild to moderate impairment of kidney function were included in the study. Thirteen of them suffered from IR. Their dietary protein intake was decreased from > or = 1.0 g/kg/d to 0.6-0.7 g/kg/d. Moreover, they were treated by ACEI enalapril at dosages of 2-10 mg/d depending on the absence/presence and severity of hypertension. The patients were followed for 8 months. No clinically relevant kidney disease progression (KDP) was found. IR patients improved remarkably. IR was examined by the oral glucose tolerance test and glucose, insulin and C-peptide determinations. Their increased plasma triglyceride, VLDL concentrations and proteinuria decreased, HDL concentration increased. Acid-base balance and anaemia did not change. It is concluded that protein restriction in combination with ACEI treatment improve IR and the associated dyslipoproteinaemia and proteinuria.

L6 ANSWER 74 OF 166 MEDLINE on STN
ACCESSION NUMBER: 97434976 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9291199
TITLE: Autonomy of the renin system in type II diabetes mellitus: dietary sodium and renal hemodynamic responses to ACE inhibition.
AUTHOR: De'Oliveira J M; Price D A; Fisher N D; Allan D R; McKnight J A; Williams G H; Hollenberg N K
CORPORATE SOURCE: Department of Medicine, Harvard Medical School and Brigham and Women's Hospital, Boston, Massachusetts 02115, USA.
CONTRACT NUMBER: M01RR026376 (NCRR)
P01AC00059916
T32 HL-07609 (NHLBI)
+
SOURCE: Kidney international, (1997 Sep) Vol. 52, No. 3, pp. 771-7.
Journal code: 0323470. ISSN: 0085-2538.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Space Life Sciences
ENTRY MONTH: 199710
ENTRY DATE: Entered STN: 5 Nov 1997
Last Updated on STN: 5 Nov 1997
Entered Medline: 23 Oct 1997

AB Recognition that non-insulin-dependent diabetes mellitus (NIDDM) is a leading cause of end-stage renal disease (ESRD), and a focus of recent therapeutic and genetic studies on the renin system have rekindled interest in mechanisms by which angiotensin converting enzyme (ACE) inhibitors influence the diabetic kidney. We evaluated the renal hemodynamic status of 19 hypertensive patients with NIDDM under controlled sodium balance, low (10 mmol/day for 5 to 7 days) or high (200 mmol/day for 5 to 7 days). The renal plasma flow (RPF) response to ACE inhibition and to angiotensin II (Ang II) infusion was measured as para-aminohippurate (PAH) clearance before and during enalapril administration (10 mg b.i.d. for 3 days). Our premise was that if renal vasodilation induced by ACEI involves kinins, prostaglandins, and/or nitric oxide, vasoconstrictor responses to Ang II would be blunted. Conversely, if the dominant ACE inhibitor action were a reduction in Ang II formation, the consequence would be up-regulation and an enhanced vasoconstrictor response to exogenous Ang II. RPF in NIDDM on a high-salt diet was lower than in age-matched controls (477 +/- 25 vs. 551 +/- 25 ml/min/1.73 m2; P = 0.02). Enalapril increased RPF in NIDDM to 511 +/- 29 ml/min/1.73 m2 (P < 0.05) and enhanced renal vasoconstrictor responses to Ang II infusion, from -68 +/- 9 to -106 +/- 18 ml/min/1.73 m2 (P = 0.03). Baseline plasma renin activity (PRA) and plasma aldosterone significantly exceeded matched normotensive controls (1.1 +/- 0.5 vs. 0.3 +/- 0.1 ng AI/ml/hr and 10 +/- 0.9 vs. 4.1 +/- 0.5 ng/dl, P < 0.01, respectively). Conversely all measures in studies on a low-salt diet were normal. Our findings indicate that: (1) NIDDM with hypertension is associated with reduced RPF when dietary salt intake is high, (2) reduced Ang II formation is the dominant mechanism of ACEI-induced renal vasodilation in hypertensives with NIDDM; and (3) the sustained renal hemodynamic responses to ACE inhibition despite high-salt balance, and the increased PRA suggest an autonomous renin-angiotensin system suppressed subnormally by a high salt diet in patients with NIDDM despite greater volume expansion.

L6 ANSWER 75 OF 166 MEDLINE on STN
ACCESSION NUMBER: 97383430 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9239450
TITLE: Possible involvement of ATP-dependent K-channel related mechanisms in the antihypertensive and cough suppressant effects of the novel ACE inhibitor (2S, 3aS, 7aS)-1-(N2-nicotinoyl-L-lysyl-gamma-D-glutamyl)octahydro-1H-indole-2-carboxylic acid.
AUTHOR: Nagata S; Takeyama K; Hosoki K; Karasawa T
CORPORATE SOURCE: Department of Pharmacology I, Dainippon Pharmaceutical Co., Ltd., Osaka, Japan.
SOURCE: Arzneimittel-Forschung, (1997 Jun) Vol. 47, No. 6, pp. 726-30.
Journal code: 0372660. ISSN: 0004-4172.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199709
ENTRY DATE: Entered STN: 16 Sep 1997
Last Updated on STN: 6 Feb 1998
Entered Medline: 4 Sep 1997

AB The antihypertensive and cough suppressant mechanisms of DU-1777 ((2S,3aS,7aS)-1-(N2-nicotinoyl-L-lsyl-gamma-D-glutamyl)octahydro-1H-indole-2 -carboxylic acid, CAS 116662-73-8), a new long-acting angiotensin-1-converting enzyme (ACE) inhibitor, were investigated in vivo and in vitro. The antihypertensive effects of DU-1777 at 10 mg/kg p.o. and cromakalim at 0.3 mg/kg p.o. were partially (about 60%) or fully antagonized by glibenclamide at 10 mg/kg i.v. in 2-kidney, 1-clip renal hypertensive rats (2K-1C RHR). The antihypertensive effects of a Ca blocker (nifedipine) and other ACE inhibitors (captopril, alacepril, enalapril, lisinopril, imidapril and quanapril) were not antagonized by glibenclamide. In deoxycorticosterone acetate-salt hypertensive rats (DOCA-HR), the antihypertensive effects of DU-1777 at 3-30 mg/kg p.o. were fully antagonized by glibenclamide. However, in vitro, DU-1777 (10(-6)-10(-3) mol/l) did not affect aortic ring contractions induced by high K (30 mmol/l). In guinea pig, citric acid induced cough was increased by ACE inhibitors, captopril, alacepril, enalapril and lisinopril (10 and 30 mg/kg p.o.). DU-1777 had a tendency to decrease citric acid induced cough and the effect was antagonized by glibenclamide. These results suggest that while DU-1777 itself does not open ATP-dependent K channel, it indirectly produces these effects through unknown mechanisms in vivo. Moreover, these effects contributed to the antihypertensive effect in DOCA-HR and cough suppressant effect in guinea pigs.

L6 ANSWER 76 OF 166 MEDLINE on STN
ACCESSION NUMBER: 97304424 . MEDLINE
DOCUMENT NUMBER: PubMed ID: 9160787
TITLE: Long-term infusion of kallikrein attenuates renal injury in Dahl salt-sensitive rats.
AUTHOR: Uehara Y; Hirawa N; Numabe A; Kawabata Y; Ikeda T; Gomi T; Gotoh A; Omata M
CORPORATE SOURCE: Second Department of Medicine, University of Tokyo, Bunkyo-ku, Japan.. UEHARA-2IM@h.u-tokyo.ac.jp
SOURCE: American journal of hypertension : journal of the American Society of Hypertension, (1997 May) Vol. 10, No. 5 Pt 2, pp. 83S-88S. Ref: 23
Journal code: 8803676. ISSN: 0895-7061.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199707
ENTRY DATE: Entered STN: 24 Jul 1997
Last Updated on STN: 3 Mar 2000
Entered Medline: 17 Jul 1997

AB We investigated whether long-term infusion of kallikrein would attenuate renal injury in salt-induced hypertension in Dahl salt-sensitive (Dahl S) rats. A subdepressor dose of purified rat urinary kallikrein (RUK) (700 ng/day) was infused intravenously by an osmotic minipump for 4 weeks in male Dahl S rats fed a high-salt (2% NaCl) diet. This dose did not affect the time-dependent elevation of blood pressure. However, urinary protein excretion was significantly decreased, and the glomerular filtration rate was increased. These beneficial effects were reflected morphologically by an attenuation of the glomerulosclerotic lesions and tubular injury seen in the hypertensive Dahl S rats. The kallikrein infusion increased the urinary excretion of bradykinin and stimulated the excretion of cyclic GMP, suggesting that the kallikrein-kinin-prostaglandin and nitric oxide axes were enhanced by the RUK infusion. The alterations induced by such infusion were potentiated by the concomitant administration of the angiotensin converting enzyme inhibitor alacepril. These studies indicated that long-term replacement with rat tissue kallikrein attenuates renal injury in hypertensive Dahl S rats, and this is probably mediated by an enhanced

function of the kallikrein-kinin-prostaglandin and nitric oxide systems.

L6 ANSWER 77 OF 166 MEDLINE on STN
ACCESSION NUMBER: 97234407 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9079232
TITLE: Pharmacological and toxicological studies of the new angiotensin converting enzyme inhibitor moexipril hydrochloride.
AUTHOR: Friehe H; Ney P
CORPORATE SOURCE: Department of Pharmacology and Toxicology, Schwarz Pharma AG, Monheim, Germany.
SOURCE: Arzneimittel-Forschung, (1997 Feb) Vol. 47, No. 2, pp. 132-44.
Journal code: 0372660. ISSN: 0004-4172.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199705
ENTRY DATE: Entered STN: 7 May 1997
Last Updated on STN: 7 May 1997
Entered Medline: 1 May 1997

AB The pharmacodynamic and toxicological profile of the new angiotensin converting enzyme (ACE) inhibitor moexipril (CAS 82586-52-5) and its active diacid metabolite moexiprilat were studied in vitro as well as in vivo. In vitro, moexiprilat was a potent inhibitor of ACE in guinea pig serum as well as on purified ACE from rabbit lung with IC50 values of 2.6 and 4.9 nmol/l, respectively. Both, moexipril and moexiprilat inhibited the angiotensin I (ANG I)-induced contractions of rabbit aorta concentration-dependently, whereas contractions by other agents were not affected, indicating a high selectivity of both compounds for ACE. Similar results were obtained in vivo in experiments investigating the blood pressure increasing response to intravenous injection of ANG I or ANG II in conscious normotensive rats and dogs after oral or intravenous application of moexipril or moexiprilat, respectively. The antihypertensive effects of the oral application of moexipril were studied in models of hypertension in the rat as well as in renal hypertensive dogs. In renal hypertensive rats, moexipril (0.03-10 mg/kg p.o.) caused a dose-dependent decrease in blood pressure with a threshold dose of 0.3 mg/kg. Once daily treatment of the animals with 3 mg/kg/d for 5 days lowered mean blood pressure by about 70 mmHg and blood pressure was maintained on this low level for the experimental period. In spontaneously hypertensive rats, oral administration of moexipril (30 mg/kg/d) for 5 days caused a progressive lowering of mean blood pressure from pre-treatment values of 180 +/- 7 mmHg to a trough on day 4 of 127 +/- 4 mmHg. In perinephritic hypertensive dogs, oral administration of moexipril (10 mg/kg) in combination with hydrochlorothiazide (10 mg/kg) caused a drop of mean blood pressure by 25 mmHg from pre-treatment control, which persisted for 24 h. In all these models, the action was characterized by a rapid onset and a long duration of action. After cessation of treatment, a gradual return to baseline values was observed. In contrast, only slight blood pressure lowering effects were seen in normotensive rats at high doses (100 mg/kg p.o.). The general pharmacological properties of moexipril were also studied in generally accepted models in vitro and in vivo. In doses or concentrations more than 100 times higher than those causing ACE inhibition, no effects were observed on the central nervous system, on isolated smooth muscle preparations, the digestive system, the kidney or the lung. Additionally, moexipril is devoid of anti-inflammatory properties and has no effect on platelet function. On the cardiovascular system, the effects observed can be attributed to ACE inhibition by moexipril. Repeated dose toxicity studies in rats and dogs revealed the heart and kidneys as target organs.

These effects, based on highly exaggerated pharmacological activity, are comparable to other ACE-inhibitors. No potential for mutagenic or carcinogenic activity and no evidence of reproductive toxicity was apparent for meoxipril. The preclinical data indicate that moexipril possesses a high degree of specifity as an ACE-inhibitor without relevant side effects or gross toxicity.

L6 ANSWER 78 OF 166 MEDLINE on STN
ACCESSION NUMBER: 97222240 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9124472
TITLE: Enalapril and captopril enhance antioxidant defenses in mouse tissues.
AUTHOR: de Cavanagh E M; Fraga C G; Ferder L; Inserra F
CORPORATE SOURCE: Department of Physical Chemistry, School of Pharmacy and Biochemistry, University of Buenos Aires, Argentina.
SOURCE: The American journal of physiology, (1997 Feb) Vol. 272, No. 2 Pt 2, pp. R514-8.
Journal code: 0370511. ISSN: 0002-9513.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199704
ENTRY DATE: Entered STN: 6 May 1997
Last Updated on STN: 29 Jan 1999
Entered Medline: 22 Apr 1997
AB This study was conducted to investigate a possible systemic effect of angiotensin-converting enzyme inhibitors (ACEi) on tissue antioxidant defenses. CF1 mice (4-mo-old females) were administered either water (control) or water containing enalapril (20 mg/l) or captopril (50 mg/l) during 11 wk. Neither enalapril nor captopril treatment had an effect on body mass or brain, kidney, or heart weight relative to controls. CuZn-superoxide dismutase (SOD) activity was increased by enalapril treatment in kidney medulla (27%), heart (24%), and erythrocytes (19%) and by captopril treatment in kidney medulla (43%) and heart (54%) relative to controls. Mn-SOD and catalase activities were unaffected by either treatment. Enalapril, but not captopril treatment, increased Se-glutathione peroxidase activity in renal medulla (19%). Nonenzymatic antioxidant defenses, evaluated by tert-butyl hydroperoxide-initiated chemiluminescence (HICL), were enhanced in kidney cortex (48%) by enalapril and in brain by enalapril (44%) or captopril (36%) treatment relative to controls. As evaluated in vitro by HICL and thiobarbituric acid-reactive substances formation, captopril had a free radical scavenger activity, whereas neither enalapril nor lisinopril was effective. These results suggest that ACEi may protect tissues from oxidative damage by increasing enzymatic and nonenzymatic antioxidant defenses.

L6 ANSWER 79 OF 166 MEDLINE on STN
ACCESSION NUMBER: 97197076 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9044165
TITLE: Tubular transport mechanisms of quinapril and quinaprilat in the isolated perfused rat kidney: effect of organic anions and cations.
AUTHOR: Kugler A R; Olson S C; Smith D E
CORPORATE SOURCE: Department of Pharmacokinetics and Drug Metabolism, Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, Ann Arbor, Michigan 48106-1047, USA.
CONTRACT NUMBER: R01 GM35498 (NIGMS)
SOURCE: Journal of pharmacokinetics and biopharmaceutics, (1996 Aug) Vol. 24, No. 4, pp. 349-68.
Journal code: 0357115. ISSN: 0090-466X.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199705
ENTRY DATE: Entered STN: 7 May 1997
Last Updated on STN: 7 May 1997
Entered Medline: 1 May 1997

AB The clearance mechanisms of quinapril and quinaprilat were probed using an isolated perfused rat kidney model. Sixty-four experiments were performed with drug in the absence and presence of classic inhibitors of the organic acid (i.e., probenecid and p-aminohippurate) and organic base (i.e., tetraethylammonium and quinine) transport systems of the proximal tubule. Initial perfusate concentrations of quinapril and quinaprilat were approximately 2.36 microM (or 1000 ng/ml), and transport inhibitors were coperfused at 100-10,000 times the drugs' initial microM concentrations. Quinapril and quinaprilat concentrations were determined in perfusate, urine, and perfusate ultrafiltrate using a reversed-phase HPLC procedure with radiochemical detection, coupled to liquid scintillation spectrometry. Perfusate protein binding was determined using an ultrafiltration method at 37 degrees C. Overall, the clearance ratios of quinapril (total renal clearance divided by fu x GFR) and quinaprilat (urinary clearance divided by fu. GFR) were significantly reduced, and in a dose-dependent manner,. by the coperfusion of organic acids but not organic bases. The data demonstrate that the organic anionic secretory system is the primary mechanism by which quinapril and quinaprilat are transported into and across renal proximal cells.

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L6 ANSWER 60 OF 166 MEDLINE on STN
ACCESSION NUMBER: 2000166665 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10703899
TITLE: Effects of alacepril and amlodipine on the renal injury induced by a high-cholesterol diet in rats.
AUTHOR: Atarashi K; Takagi M; Minami M; Ishiyama A
CORPORATE SOURCE: The Second Department of Internal Medicine, Faculty of Medicine, University of Tokyo, Japan.
SOURCE: Journal of hypertension, (1999 Dec) Vol. 17, No. 12 Pt 2, pp. 1983-6.
Journal code: 8306882. ISSN: 0263-6352.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200003
ENTRY DATE: Entered STN: 27 Mar 2000
Last Updated on STN: 27 Mar 2000
Entered Medline: 16 Mar 2000

AB BACKGROUND: A high-cholesterol (HC) diet increases blood pressure and induces renal injury in rats. We compared the effects of alacepril, an ACE inhibitor, and amlodipine, a Ca antagonist, on the renal injury induced by an HC diet in rats. DESIGN AND METHODS: Male Sprague-Dawley rats were given either an HC diet only (n = 5), an HC diet and amlodipine (n = 10) or an HC diet and alacepril (n = 10). The control rats (n = 5) were given a normal diet Systolic blood pressure (SBP) was measured by a tail-cuff method. Serum lipids, malondialdehyde (MDA) as a parameter for lipid peroxidation and urinary protein excretion were determined at 0, 4 and 8 weeks. The renal injury was evaluated histologically by the glomeruli sclerosing score. RESULTS: The HC diet increased SBP. Amlodipine lowered SBP more

significantly than alacepril. Serum total cholesterol was increased by the HC diet and was not affected by either anti-hypertensive agent. HDL-cholesterol was similarly decreased in the three HC diet groups. Alacepril, but not amlodipine, completely attenuated the MDA elevation induced by the HC diet. Urinary protein excretion was decreased by the two anti-hypertensive agents at a similar rate. The renal histological injury assessed by the sclerosing score was ameliorated more significantly by alacepril than by amlodipine. CONCLUSIONS: Both amlodipine and alacepril decreased blood pressure and urinary protein, and ameliorated the renal injury induced by the HC diet in rats. The renal effect of alacepril seems to be mediated by the decrease in oxidative stress as well as by reduction of blood pressure, since alacepril lowered the sclerosing score more than amlodipine and completely attenuated MDA, although the blood pressure reduction by alacepril was less than that by amlodipine.

L6 ANSWER 61 OF 166 MEDLINE on STN
ACCESSION NUMBER: 2000160767 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10694829
TITLE: Does Chinese ethnicity affect the pharmacokinetics and pharmacodynamics of angiotensin-converting enzyme inhibitors?.
AUTHOR: Ding P Y; Hu O Y; Pool P E; Liao W
CORPORATE SOURCE: Department of Internal Medicine, Veterans General Hospital-Taipei, Taipei, Taiwan, Republic of China.
SOURCE: Journal of human hypertension, (2000 Mar) Vol. 14, No. 3, pp. 163-70. Ref: 53
Journal code: 8811625. ISSN: 0950-9240.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200003
ENTRY DATE: Entered STN: 7 Apr 2000
Last Updated on STN: 7 Apr 2000
Entered Medline: 30 Mar 2000

AB Information from clinical and pharmacokinetic studies of angiotensin-converting enzyme inhibitors (ACEIs) has come from subjects who are mostly male and Caucasian, but the use of ACEIs extends to populations worldwide. Significant differences between Chinese in general and male Caucasians have been demonstrated in the pharmacokinetics/dynamics of other drug classes that could have implications for the use of ACEIs in the Chinese population. These include: significant Chinese/Caucasian genetic variation in the renin-angiotensin system based on an insertion/deletion (O/D) polymorphism of the ACE gene; the genetic determination of plasma ACE activity in the Chinese population; and genetic factors involving the disease substrate which may also influence the response to treatment. Oral and IV pharmacokinetic data from various studies of Chinese and Caucasian subjects are available for cilazapril, fosinopril, and perindopril, and pharmacodynamic data are available for eight different ACEIs. Based on these data, there are few differences among the pharmacokinetics of ACEIs between Chinese and Caucasians. Most ACEIs showed good blood pressure lowering efficacy in Chinese (benazepril, enalapril, fosinopril and spirapril), with perhaps less blood pressure lowering with cilazapril or a relatively shorter-term effect with cilazapril or perindopril compared to Caucasions. Chinese experience more cough from ACEIs (captopril and enalapril) than Caucasians. Data suggest that fosinopril may not induce cough in as many subjects as other ACEIs, and this seems to be true of Chinese as well. The mechanism, currently unknown, could involve fosinopril's dual elimination pathway (hepatic and renal). Pharmacokinetic data

also support the use of fosinopril in congestive heart failure where elimination pathways may be impaired. In conclusion, ethnic differences between Chinese and Caucasians with respect to ACE and AGT gene polymorphism, which might be expected to differentially affect the action of ACEIs in these two ethnic groups, do not, in fact, have such an effect. Rather, differences among the ACEIs appear to be more important. Journal of Human Hypertension (2000) 14, 163-170.

L6 ANSWER 62 OF 166 MEDLINE on STN
ACCESSION NUMBER: 2000153669 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10688628
TITLE: New insights on effect of kidney insufficiency on disposition of angiotensin-converting enzyme inhibitors: case of enalapril and benazepril in dogs.
AUTHOR: Toutain P L; Lefebvre H P; Laroute V
CORPORATE SOURCE: Ecole Nationale Veterinaire de Toulouse, et Institut National de la Recherche Agronomique, Unite Associee de Physiopathologie et Toxicologie Experimentales, Toulouse, France.. pl.toutain@envt.fr
SOURCE: The Journal of pharmacology and experimental therapeutics, (2000 Mar) Vol. 292, No. 3, pp. 1094-103.
Journal code: 0376362. ISSN: 0022-3565.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200003
ENTRY DATE: Entered STN: 30 Mar 2000
Last Updated on STN: 30 Mar 2000
Entered Medline: 17 Mar 2000

AB The influence of a renal injury on the disposition of benazeprilat, the active moiety of benazepril, and of enalaprilat, the active moiety of enalapril, two angiotensin-converting enzyme (ACE) inhibitors (ACEI), having different routes of elimination in dog was investigated during a mild renal insufficiency obtained by a nephrectomy-electrocoagulation method reducing glomerular filtration rate by approximately 50%. Plasma concentrations of the active moieties were analyzed with a physiologically based model taking into account the binding to ACE (high affinity, low capacity). An influence of renal insufficiency on enalapril disposition was shown with an increase in its plasma concentration, which was correlated to the reduction of the glomerular filtration rate. No such effect was evidenced for benazepril. With the physiologically based model analysis, it was shown that renal impairment led to an increase of the apparent benazeprilat clearance (260%), whereas that of enalaprilat was reduced to 40 to 55%. Renal insufficiency had no significant effect either on the apparent volume of distribution of each drug or on the binding parameters [i.e., maximal binding capacity (B(max)) and affinity (K(d))]. Enalaprilat and benazeprilat inhibitory action on ACE also was evaluated ex vivo. Similar patterns of inhibition were observed for both drugs. Renal injury had no significant influence on the overall effect of benazeprilat, whereas the inhibition effect of enalaprilat was significantly increased. It was concluded that renal insufficiency may have effects on the ACEI disposition but that the measurable active moiety plasma concentration is not the most appropriate endpoint to describe and interpret the consequence of a renal injury on ACEI.

L6 ANSWER 63 OF 166 MEDLINE on STN
ACCESSION NUMBER: 1999436711 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10506823
TITLE: [Comparative study of the reno-protective effect of short- and long-acting antihypertensive agents in IgA nephropathy].

A rovid es a hosszu hatasu antihypertensiv szerek renoprotective hatasanak osszehasonlito vizsgalata IgA nephropathias betegekben.

AUTHOR: Vas T; Kovacs T; Szelestei T; Csiky B; Nagy J

CORPORATE SOURCE: II. sz. Belgyogyaszati Klinika, Pecsi Orvostudomanyi Egyetem.

SOURCE: Orvosi hetilap, (1999 Sep 5) Vol. 140, No. 36, pp. 1991-5. Journal code: 0376412. ISSN: 0030-6002.

PUB. COUNTRY: Hungary

DOCUMENT TYPE: (CLINICAL TRIAL) Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: Hungarian

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199910

ENTRY DATE: Entered STN: 14 Oct 1999
Last Updated on STN: 14 Oct 1999
Entered Medline: 6 Oct 1999

AB The progression of IgA-NP is influenced unfavourably by development and existence of hypertension. The treatment of hypertension (HTN) has an important role in these patients. Both short- and long-acting formulations of angiotensin convertase enzim inhibitors (ACEi) and calcium channel blockers (CCB) lower blood-pressure, however long-acting preparations may provide better control and may have more renoprotective effect. Verifying this hypothesis, 22 IgA-NP patients were followed for 7.25 +/- 2.36 years. The patients were on short-acting ACEi (captopril, n = 9) or dihydropyridine type CCB (nifedipin, n = 2) or both (captopril + nifedipine n = 11), after at least 3 years the medication was changed to long-acting ACEI (enalapril, n = 4; cilazapril, n = 1), or non dihydropyridine type CCB (diltiazem hydrochlorid, n = 1) or both (n = 16). Just before changing the medication these patients underwent 24 hour ambulatory blood pressure monitoring and at the same time the level of proteinuria and the creatine clearance were measured. Values of serum-creatinine were measured in every 3-4 months within a 3 years period before and after the exchange of antihypertensive drugs. The regression of 1/creatinine was a = -5.28.10(-5) +/- 1.16.10(-4) before and a = 1.03.10(-4) +/- 2.05.10(-4) after the change of medication. Using paired t-test there was a significant difference between the regressions of 1/creatine ($p < 0.005$). Systolic blood pressure (SBP) (128 +/- 81 Hgmm vs. 126.09 +/- 11.67 Hgmm) was not different, however, diastolic blood pressure (DBP) (84.15 +/- 7.94 Hgmm vs. 79.78 +/- 7.17 Hgmm), diastolic percent time elevation index (HTI) (43.58 +/- 23.57% vs. 25.61 +/- 20.1%) and 24-hour diastolic hyperbaric impact (114.71 +/- 81.9 vs. 51.51 +/- 51.4, $p < 0.05$) was lower with long-acting antihypertensive agents, as was the proteinuria (1.18 +/- 0.94 g/die vs. 0.69 +/- 1.08 g/die, $p < 0.05$). Diurnal variation and systolic percent time elevation index were not different. We conclude that long-acting ACEi and non dihydropyridine type CCB formulations result in better outcomes in IgA nephropathy patients compared to short-acting drugs, probably because of better and smoother blood pressure control, lowering of proteinuria and better compliance of the patients.

L6 ANSWER 64 OF 166 MEDLINE on STN

ACCESSION NUMBER: 1999400355 MEDLINE

DOCUMENT NUMBER: PubMed ID: 10469854

TITLE: Higher levels of antioxidant defenses in enalapril -treated versus non-enalapril-treated hemodialysis patients.

AUTHOR: de Cavanagh E M; Ferder L; Carrasquedo F; Scrivo D; Wassermann A; Fraga C G; Inserra F

CORPORATE SOURCE: Department of Experimental Nephrology, School of Pharmacy and Biochemistry, Buenos Aires, Argentina.

SOURCE: American journal of kidney diseases : the official journal of the National Kidney Foundation, (1999 Sep) Vol. 34, No.

3, pp. 445-55.
Journal code: 8110075. E-ISSN: 1523-6838.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
(CONTROLLED CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199909
ENTRY DATE: Entered STN: 5 Oct 1999
Last Updated on STN: 21 May 2001
Entered Medline: 21 Sep 1999

AB We previously reported chronic treatment with angiotensin-converting enzyme inhibitors (ACEis) increases antioxidant defenses in mice. In the present study, however, we examined various antioxidant defenses in chronic hemodialysis (HD) patients either treated with enalapril (10 mg/d) for at least 6 months (+ACEi; n = 11) or untreated (-ACEi; n = 11). The relationship between antioxidant status and HD was investigated by determining oxidative stress markers and antioxidant defenses in a group of chronic HD patients (n = 33) and a group of age-matched controls (n = 29). The effect of a single HD session on those parameters was also evaluated. Before an HD session (pre-HD), HD patients had significantly lower levels of red blood cell (RBC) glutathione (GSH), selenium-dependent glutathione peroxidase activity (RBC-Se-GPx), plasma ubiquinol-10, and alpha-tocopherol than controls. In a randomly selected group of patients (n = 19), a single HD session caused an additional decrease in RBC-GSH and plasma ubiquinol-10 levels. Plasma thiobarbituric acid reactive substance (TBARS) levels were significantly greater in pre-HD patients than controls. Post-HD plasma TBARS levels were similar to control values. The cohort of +ACEi HD patients had greater pre-HD RBC-GSH content, RBC-Se-GPx activity, and plasma beta-carotene concentrations than -ACEi patients (RBC-GSH: +ACEi, 3.1 +/- 0.9 micromol/mL packed RBCs [PRBCs]; -ACEi, 1.2 +/- 0.3 micromol/mL PRBCs [P < 0.05 v +ACEi]; RBC-Se-GPx: +ACEi, 5.8 +/- 0.7 U/mL PRBCs; -ACEi, 4.3 +/- 0.2 U/mL PRBCs [P < 0.05 v +ACEi]; plasma beta-carotene: +ACEi, 0.54 +/- 0.16 micromol/L plasma; -ACEi, 0.19 +/- 0.05 micromol/L plasma [P < 0.05 v +ACEi]). Results show profound alterations in the circulating antioxidant systems of chronic HD patients and that additional oxidative stress occurs during the HD procedure. In addition, in +ACEi HD patients, the levels of several antioxidant defenses are greater than in those in -ACEi HD patients.

L6 ANSWER 65 OF 166 MEDLINE on STN
ACCESSION NUMBER: 1999398519 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10469358
TITLE: Effect of candesartan cilexetil (TCV-116) in rats with chronic renal failure.
AUTHOR: Noda M; Matsuo T; Fukuda R; Ohta M; Nagano H; Shibouta Y; Naka T; Nishikawa K; Imura Y
CORPORATE SOURCE: Pharmaceutical Research Laboratories II, Pharmaceutical Research Division, Takeda Chemical Industries, Ltd., Osaka, Japan.. Noda_Masakuni@takeda.co.jp
SOURCE: Kidney international, (1999 Sep) Vol. 56, No. 3, pp. 898-909.
Journal code: 0323470. ISSN: 0085-2538.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199910
ENTRY DATE: Entered STN: 1 Nov 1999
Last Updated on STN: 13 Mar 2003

Entered Medline: 21 Oct 1999

AB BACKGROUND: Inhibition of the renin-angiotensin system by both angiotensin II type 1 receptor antagonists (AT1As) and angiotensin I-converting enzyme inhibitors (ACEIs) shows renoprotective effects in rats with chronic renal failure when treatment is started in the early phase of renal injury. In this study, we examined the renal protective effects of candesartan cilexetil (TCV-116), an AT1A, and enalapril, an ACEI, in the progressive phase of renal injury in 5/6 nephrectomized rats. METHODS: Candesartan cilexetil (1 mg/kg/day) and enalapril (10 mg/kg/day) were orally administered once a day for 4 weeks (the short-term experiment) or 16 weeks (the long-term experiment) to 5/6 nephrectomized rats beginning 15 weeks after the nephrectomy, that is, after they had already showed marked proteinuria. RESULTS: In vehicle-treated rats, proteinuria, glomerulosclerosis, and interstitial fibrosis developed. Moreover, enhanced expression of transforming growth factor-beta1 (TGF-beta1) in the injured glomeruli was observed. These adverse changes progressed with time, and in the short-term experiment, both drugs inhibited them. In the long-term experiment, the progressive proteinuria and the elevation of blood pressure were similarly attenuated by both drugs. However, candesartan cilexetil significantly inhibited the progression of glomerulosclerosis, the expression of TGF-beta1, and interstitial fibrosis, whereas enalapril did not. CONCLUSION: These results indicate that candesartan cilexetil shows potent and long-term preventive effects against the progression of previously developed renal injury.

L6 ANSWER 66 OF 166 MEDLINE on STN
ACCESSION NUMBER: 1999332111 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10405200
TITLE: Converting enzyme inhibition and the glomerular hemodynamic response to glycine in diabetic rats.
AUTHOR: Slomowitz L A; Peterson O W; Thomson S C
CORPORATE SOURCE: Baylor School of Medicine, Houston, Texas, USA.
SOURCE: Journal of the American Society of Nephrology : JASN, (1999 Jul) Vol. 10, No. 7, pp. 1447-54.
Journal code: 9013836. ISSN: 1046-6673.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199909
ENTRY DATE: Entered STN: 13 Sep 1999
Last Updated on STN: 13 Sep 1999
Entered Medline: 2 Sep 1999

AB GFR normally increases during glycine infusion. This response is absent in humans and rats with established diabetes mellitus. In diabetic patients, angiotensin-converting enzyme inhibition (ACEI) restores the effect of glycine on GFR. To ascertain the glomerular hemodynamic basis for this effect of ACEI, micropuncture studies were performed in male Wistar-Froemter rats after 5 to 6 wk of insulin-treated streptozotocin diabetes. The determinants of single-nephron GFR (SNGFR) were assessed in each rat before and during glycine infusion. Studies were performed in diabetics, diabetics after 5 d of ACEI (enalapril in the drinking water), and weight-matched controls. Diabetic rats manifest renal hypertrophy and glomerular hyperfiltration but not glomerular capillary hypertension. ACEI reduced glomerular capillary pressure, increased glomerular ultrafiltration coefficient, and did not mitigate hyperfiltration. In controls, glycine increased SNGFR by 30% due to increased nephron plasma flow. In diabetics, glycine had no effect on any determinant of SNGFR. In ACEI-treated diabetics, the SNGFR response to glycine was indistinguishable from nondiabetics, but the effect of glycine was mediated by greater ultrafiltration pressure rather

than by greater plasma flow. These findings demonstrate that: (1) The absent response to glycine in established diabetes does not indicate that renal functional reserve is exhausted by hyperfiltration; and (2) ACEI restores the GFR response to glycine in established diabetes, but this response is mediated by increased ultrafiltration pressure rather than by increased nephron plasma flow.

L6 ANSWER 67 OF 166 MEDLINE on STN
ACCESSION NUMBER: 1999277503 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10350000
TITLE: Competitive inhibition of glycylsarcosine transport by enalapril in rabbit renal brush border membrane vesicles: interaction of ACE inhibitors with high-affinity H+/peptide symporter.
AUTHOR: Lin C J; Akarawut W; Smith D E
CORPORATE SOURCE: College of Pharmacy and Upjohn Center for Clinical Pharmacology, The University of Michigan, Ann Arbor 48109, USA.
CONTRACT NUMBER: R01 GM35498 (NIGMS)
SOURCE: Pharmaceutical research, (1999 May) Vol. 16, No. 5, pp. 609-15.
Journal code: 8406521. ISSN: 0724-8741.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199907
ENTRY DATE: Entered STN: 30 Jul 1999
Last Updated on STN: 30 Jul 1999
Entered Medline: 16 Jul 1999
AB PURPOSE: To examine the inhibitory potential of enalapril [and other angiotensin converting enzyme (ACE) inhibitors] on glycylsarcosine (GlySar) transport by the high-affinity renal peptide transporter. METHODS: Studies were performed in rabbit renal brush border membrane vesicles in which the uptake of radiolabeled GlySar was examined in the absence and presence of captopril, enalapril, enalaprilat, fosinopril, lisinopril, quinapril, quinaprilat, ramipril and zofenopril. RESULTS: Kinetic analyses demonstrated that enalapril inhibited the uptake of GlySar in a competitive manner (Ki approximately 6 mM). Fosinopril and zofenopril had the greatest inhibitory potency (IC50 values of 55 and 81 microM, respectively) while the other ACE inhibitors exhibited low-affinity interactions with the renal peptide transporter. With respect to structure-function, ACE inhibitor affinity was strongly correlated with drug lipophilicity ($r = 0.944$, $p < 0.001$ for all ACE inhibitors; $r = 0.983$, $p < 0.001$ without enalaprilat, quinaprilat and quinapril). CONCLUSIONS: The data suggest that enalapril and GlySar compete for the same substrate-binding site on the high-affinity peptide transporter in kidney, and that ACE inhibitors can interact with the renal carrier and inhibit dipeptide transport.

L6 ANSWER 68 OF 166 MEDLINE on STN
ACCESSION NUMBER: 1998281419 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9620109
TITLE: Pharmacologic, pharmacokinetic, and therapeutic differences among ACE inhibitors.
AUTHOR: White C M
CORPORATE SOURCE: School of Pharmacy, University of Connecticut, Storrs, USA.
SOURCE: Pharmacotherapy, (1998 May-Jun) Vol. 18, No. 3, pp. 588-99.
Ref: 84
Journal code: 8111305. ISSN: 0277-0008.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199807
ENTRY DATE: Entered STN: 23 Jul 1998
Last Updated on STN: 23 Jul 1998
Entered Medline: 13 Jul 1998

AB Angiotensin-converting enzyme (ACE) inhibitors are a heterogeneous group of agents, and important pharmacologic, pharmacokinetic, and therapeutic differences among them must be understood to obtain optimal therapy. For patients with severe liver disease, lisinopril and captopril are not prodrugs (e.g., do not require hepatic activation), and lisinopril has almost solely renal elimination. Enalaprilat, the intravenous formulation of enalapril, is the only intravenously available ACE inhibitor and can be given to patients with severe liver dysfunction as it is also not a prodrug. Fosinopril is the only drug with compensatory dual routes of elimination, and it does not require dosage adjustment in patients with reduced renal function, as other ACE inhibitors do. Captopril and moexipril have potential drug-food interactions and are the only agents that should be spaced from meals. The ACE inhibitors also differ in their dialyzability, half-life, lipophilicity, trough:peak ratios, approved indications, and therapeutic information available for many indications.

L6 ANSWER 69 OF 166 MEDLINE on STN
ACCESSION NUMBER: 1998271852 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9608878
TITLE: Preclinical safety studies of the combination moexipril hydrochloride/hydrochlorothiazide.
AUTHOR: Gietl R; Friehe H; Ney P
CORPORATE SOURCE: Department of Toxicology/Experimental Biology, Schwarz Pharma AG, Monheim, Germany.
SOURCE: Arzneimittel-Forschung, (1998 Apr) Vol. 48, No. 4, pp. 365-70.
Journal code: 0372660. ISSN: 0004-4172.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199807
ENTRY DATE: Entered STN: 16 Jul 1998
Last Updated on STN: 16 Jul 1998
Entered Medline: 8 Jul 1998

AB The general pharmacological properties of a combination of the angiotensin converting enzyme (ACE) inhibitor moexipril hydrochloride (CAS 82586-52-5) and the thiazide diuretic hydrochlorothiazide (CAS 58-93-5, HCTZ), ratio 7.5 + 12.5, were studied in generally accepted models in vitro and in vivo. In vitro, the combination showed neither agonistic nor antagonistic activities on the isolated guinea pig trachea in concentrations up to 2 x 10(-4) g/ml. In mice, there was no effect on intestinal motility or the thiopental-induced sleeping time up to 1000 mg/kg. The only activity observed in mice was an inhibition of spontaneous motility after oral dosing with 300 and 1000 mg/kg, respectively. Both HCTZ (1-10 mg/kg) alone and the combination moexipril/HCTZ (1.6 or 4.8 mg/kg) produced dose-related increases in diuresis and electrolyte excretion in rats, however, without any potentiating effects for the drug combination. On the cardiovascular system of anaesthetised dogs, the effects observed were as expected, e.g. dose-related decrease in blood pressure. Repeated dose toxicity studies in rats and dogs revealed the kidney as target organ. This effect, based on highly exaggerated pharmacological activity, is well-known for other ACE inhibitors. No potential for teratogenic effects could be observed for the drug combination. In summary, the preclinical data indicate that the combination of moexipril and HCTZ (ratio 7.5 + 12.5) represents a safe drug without relevant side effects or gross

toxicity.

=> dis ibib abs l6 50-59

L6 ANSWER 50 OF 166 MEDLINE on STN
ACCESSION NUMBER: 2001323744 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11097339
TITLE: Angiotensin I-converting enzyme gene polymorphism and drug response.
AUTHOR: Baudin B
CORPORATE SOURCE: Service de Biochimie A, Hopital Saint-Antoine, AP-HP, Paris, France.. bruno.baudin@sat.ap-hop-paris.fr
SOURCE: Clinical chemistry and laboratory medicine : CCLM / FESCC, (2000 Sep) Vol. 38, No. 9, pp. 853-6. Ref: 36
Journal code: 9806306. ISSN: 1434-6621.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 11 Jun 2001
Last Updated on STN: 11 Jun 2001
Entered Medline: 7 Jun 2001

AB An insertion/deletion (I/D) polymorphism of the angiotensin I-converting enzyme (ACE) gene has been described in chromosome 17q23 of the human genome. Subjects with the genotype DD have markedly higher plasma ACE levels than those with genotype II; although ACE concentration in plasma is not rate-limiting for the production of angiotensin II, it has been suggested that the renin-angiotensin system may have an enhanced role in cardiovascular homeostasis in subjects with DD genotype or D allele. Meta-analysis confirmed the association of the D allele with an increased risk of myocardial infarction and stroke, but these relations are still uncertain with longevity and renal deterioration. Otherwise, I allele seems to be related with an improved response to physical training. The I/D polymorphism of the ACE gene is not a marker for any form of hypertension, though some conflicting results have been described. Nevertheless this polymorphism may have an influence on the antihypertensive response, particularly when using ACE inhibitors (ACEI). For example, blood pressure normalization with captopril in patients suffering from cardiac failure would be more effective in II genotype; conversely, both regression in left ventricular hypertrophy and improvement in diastolic filling would be greater after long-term treatment with enalapril in patients with essential hypertension and DD genotype. Conflicting results were also described using ACEI as a renoprotective therapy. This review therefore supports the justification for further evaluation in appropriately powered studies.

L6 ANSWER 51 OF 166 MEDLINE on STN
ACCESSION NUMBER: 2001185227 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11241424
TITLE: A comparative study of morphological changes in spontaneously hypertensive rats and normotensive Wistar Kyoto rats treated with an angiotensin-converting enzyme inhibitor or a calcium-channel blocker.
AUTHOR: Saleh F H; Jurjus A R
CORPORATE SOURCE: Department of Surgery, Faculty of Medicine, The University of Sydney, Sydney, NSW 2006, Australia.. freds@medicine.usyd.edu.au
SOURCE: The Journal of pathology, (2001 Mar) Vol. 193, No. 3, pp. 415-20.
Journal code: 0204634. ISSN: 0022-3417.
PUB. COUNTRY: England: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 4 Apr 2001
Last Updated on STN: 4 Apr 2001
Entered Medline: 29 Mar 2001

AB It is not clear whether some pathological changes in hypertension are directly pressure-dependent, or hormonally induced, or both. The aortic arch has apparently never before been studied for those changes. The aim of this study was to compare the effects of controlling angiotensin II (Ang II) and/or blood pressure (BP), directly at the inception of hypertension, on the aortic arch, the left ventricle of the heart (LV), and the kidneys of spontaneously hypertensive rats (SHRs) and normotensive Wistar Kyoto (WKY) rats. An angiotensin-converting enzyme inhibitor (ACEI, enalapril) and a calcium-channel blocker (nifedipine) were used for 21 weeks. After treatment, rats were assessed for arterial plasma renin activity (PRA). The LV, aortic arch, and kidneys were then excised for the determination of organ and tissue weight in some of the animals, while in others the aortic arch was fixed in situ and processed for microscopic analysis. Both enalapril and nifedipine levelled BP in the SHRs to almost normal values. Enalapril was able to prevent the increase in LV and kidney weights ($p=0.04$ wet, $p<0.001$ dry; $p<0.001$ wet and dry, respectively) and the increase in the weight of the aortic arch and in the thickness of its media ($p<0.001$ wet and dry; $p<0.001$, respectively) seen in untreated SHRs. This was associated with a larger lumen diameter ($p<0.001$) and a lower media to lumen ratio ($p=0.01$). In contrast, nifedipine did not prevent any of the changes described. Neither nifedipine nor enalapril treatment had any effects on PRA in either rat strain. Our results support previous observations that BP is not the only factor causing some of the pathological changes in hypertension; tissue Ang II level may also play a major role.

L6 ANSWER 52 OF 166 MEDLINE on STN
ACCESSION NUMBER: 2001080636 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10981547
TITLE: Amlodipine is comparable to angiotensin-converting enzyme inhibitor for long-term renoprotection in hypertensive patients with renal dysfunction: a one-year, prospective, randomized study.
AUTHOR: Kumagai H; Hayashi K; Kumamaru H; Saruta T
CORPORATE SOURCE: Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan.
SOURCE: American journal of hypertension : journal of the American Society of Hypertension, (2000 Sep) Vol. 13, No. 9, pp. 980-5.
Journal code: 8803676. ISSN: 0895-7061.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 22 Mar 2001
Last Updated on STN: 11 May 2002
Entered Medline: 11 Jan 2001

AB Unlike angiotensin converting enzyme inhibitors (ACEI), few long-term studies have shown calcium antagonists to retard the progression of renal dysfunction. Our aim was to prospectively compare the effects of amlodipine and ACEI (enalapril) on renal function in hypertensive patients with renal impairment due to chronic glomerulonephritis and essential hypertension.

A total of 72 hypertensive patients with serum creatinine (Cr) > 1.5 mg/dL were randomly allocated to treatment with either drug. During a 1-year period, 33% of the patients treated with ACEI dropped out due to adverse events, whereas 9% of patients with amlodipine dropped out. Data of 28 patients were available for analysis of more than 1-year follow-up. Reductions in blood pressure were comparable between the amlodipine (from 165/101 to 138/81 mm Hg) and ACEI groups. Serum Cr increased from 2.1+/-0.8 (SD) to 2.6+/-1.0 mg/dL with amlodipine (n = 16), but the difference was equivalent to that with ACEI (n = 12). Creatinine clearance (Ccr) in the moderate dysfunction group (basal Cr, 1.5 to 2.0 mg/dL) changed from 36+/-10 to 33+/-11 mL/min (not significant) with amlodipine, and the change was similar to that noted with ACEI. Annual declines in Ccr with amlodipine (-3.7 mL/min/year) and ACEI (-2.6 mL/min/year) were comparable, and both tended to be smaller than the annual decline in glomerular filtration rate reported in the Modification of Diet in Renal Disease study (-6 mL/min/year). Serum potassium was increased significantly (P < .01), from 4.5+/-0.4 to 5.3+/-0.8 mEq/L, only in the ACEI group. This 1-year prospective study demonstrated the effect of amlodipine on renal function to be likely the same as that of ACEI. Furthermore, amlodipine was better tolerated than ACEI for hypertensive patients with renal dysfunction.

L6 ANSWER 53 OF 166 MEDLINE on STN
ACCESSION NUMBER: 2001078982 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11115082
TITLE: ACEI/ATRA therapy decreases proteinuria by improving glomerular permselectivity in IgA nephritis.
AUTHOR: Woo K T; Lau Y K; Wong K S; Chiang G S
CORPORATE SOURCE: Department of Renal Medicine and Department of Pathology, Singapore General Hospital, Singapore.. grmwkt@sgh.gov.sg
SOURCE: Kidney international, (2000 Dec) Vol. 58, No. 6, pp. 2485-91.
Journal code: 0323470. ISSN: 0085-2538.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 22 Mar 2001
Last Updated on STN: 22 Mar 2001
Entered Medline: 11 Jan 2001

AB BACKGROUND: It has been postulated that angiotensin-converting enzyme inhibitor/angiotensin receptor antagonist (ACEI/ATRA) may decrease proteinuria in patients with glomerulonephritis by its action on the glomerular basement membrane. We therefore studied the relationship between the response of patients with IgA nephritis (IgAN) to ACEI /ATRA therapy by decreasing proteinuria and its effect on the selectivity index (SI) in these patients. METHODS: Forty-one patients with biopsy-proven IgAN entered a control trial, with 21 in the treatment group and 20 in the control group. The entry criteria included proteinuria of 1 g or more and/or renal impairment. Patients in the treatment group received ACEI/ATRA or both with three monthly increases in dosage. In the control group, hypertension was treated with atenolol, hydrallazine, or methyldopa. The following tests were performed at three monthly intervals: serum creatinine, total urinary protein, SI, sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE), and low molecular weight (LMW) proteinuria. RESULTS: After a mean duration of therapy of 13 +/- 5 months, in the treatment group, there was no significant change in serum creatinine, proteinuria, or SI, but in the control group, serum creatinine deteriorated from 1.8 +/- 0.8 to 2.3 +/- 1.1 mg/dL (P < 0.05). Among the 21 patients in the treatment group, 10

responded to ACEI/ATRA therapy determined as a decrease in proteinuria by 30% (responders), and the other 11 did not respond (nonresponders). Among the responders, SI improved from a mean of 0.26 +/- 0.07 to 0.18 +/- 0. 07 (P < 0.001), indicating a tendency toward selective proteinuria. This was associated with an improvement in serum creatinine from mean 1.7 +/- 0.6 to 1.5 +/- 0.6 mg/dL (P < 0.02) and a decrease in proteinuria from a mean of 2.3 +/- 1.1 to 0.7 +/- 0.5 g/day (P < 0. 001). After treatment, proteinuria in the treatment group (1.8 +/- 1. 6 g/day) was significantly less than in the control group (2.9 +/- 1. 8 g/day, P < 0.05). The post-treatment SI in the responder group (0. 18 +/- 0.07) was better than that of the nonresponder group (0.33 +/- 0.11, P < 0.002). Eight out of 21 patients in the treatment group who had documented renal impairment had improved renal function compared with two in the control group (chi2 = 4.4, P < 0. 05). Of the eight patients in the treatment group who improved their renal function, three normalized their renal function compared with one from the control group. CONCLUSION: Our data suggest that ACEI/ATRA therapy may be beneficial in patients with IgAN with renal impairment and nonselective proteinuria, as such patients may respond to therapy with improvement in protein selectivity, decrease in proteinuria, and improvement in renal function. ACEI/ATRA therapy probably modifies pore size distribution by reducing the radius of large unselective pores, causing the shunt pathway to become less pronounced, resulting in less leakage of protein into the urine.

L6 ANSWER 54 OF 166 MEDLINE on STN
ACCESSION NUMBER: 2001025250 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10912779
TITLE: Renal protective effects of blocking the intrarenal renin-angiotensin system: angiotensin II type I receptor antagonist compared with angiotensin-converting enzyme inhibitor.
AUTHOR: Zhou A; Yu L; Li J; Zhang J; Wang H
CORPORATE SOURCE: Institute of Nephrology, Beijing Medical University, PR China.
SOURCE: Hypertension research : official journal of the Japanese Society of Hypertension, (2000 Jul) Vol. 23, No. 4, pp. 391-7.
Journal code: 9307690. ISSN: 0916-9636.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200011
ENTRY DATE: Entered STN: 22 Mar 2001
Last Updated on STN: 22 Mar 2001
Entered Medline: 15 Nov 2000

AB The present study compared renoprotective effects of angiotensin II type I receptor antagonist (AT1RA) with angiotensin converting enzyme inhibitor (ACEI), and their influence on the renin-angiotensin-system (RAS). Experimental nephrotic syndrome was induced in SD rats by repeated peritoneal injections of puromycin. Twenty-eight rats were randomly divided into four groups: normal control, nephrotic control, ACEI -treated, and AT1RA-treated groups. Serum, urine, and renal tissue were collected for study at the end of 12 weeks. Compared with those of the nephrotic control group, urinary protein was less and renal function was better in both treated groups. The glomerular and interstitial damage indexes of both ACEI- and AT1RA-treated rats were lower than those of nephrotic control rats, with no significant difference observed between the two treated groups. Local renal ACE activity and angiotensin II concentration were elevated in nephrotic rats (p< 0.01). However, there is no significant difference in circulating RAS, renal tissue renin, and aldosterone between the

normal control and nephrotic control rats. As expected, enalapril inhibited the local renal ACE activity and significantly decreased angiotensin II ($p < 0.01$). Intrarenal ACE activity and angiotensin concentration returned to normal levels after treatment with irbesartan ($p < 0.01$). In conclusion, AT1RA and ACEI have comparable renal protective effects, and these protective effects were associated with the inhibition of intrarenal ANG II.

L6 ANSWER 55 OF 166 MEDLINE on STN
ACCESSION NUMBER: 2000417267 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10830252
TITLE: Risk-benefit ratio of angiotensin antagonists versus ACE inhibitors in end-stage renal disease.
AUTHOR: Sica D A; Gehr T W; Fernandez A
CORPORATE SOURCE: Division of Clinical Pharmacology, Medical College of Virginia of Virginia Commonwealth University, Richmond 23298-0160, USA.. dsica@hsc.vcu.edu
SOURCE: Drug safety : an international journal of medical toxicology and drug experience, (2000 May) Vol. 22, No. 5, pp. 350-60. Ref: 101
Journal code: 9002928. ISSN: 0114-5916.
PUB. COUNTRY: New Zealand
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 15 Sep 2000
Last Updated on STN: 15 Sep 2000
Entered Medline: 1 Sep 2000

AB The effective treatment of hypertension is an extremely important consideration in patients with end-stage renal disease (ESRD). Virtually any drug class--with the possible exception of diuretics--can be used to treat hypertension in the patient with ESRD. Despite there being such a wide range of treatment options, drugs which interrupt the renin-angiotensin axis are generally suggested as agents of choice in this population, even though the evidence in support of their preferential use is quite scanty. ACE inhibitors, and more recently angiotensin antagonists, are the 2 drug classes most commonly employed to alter renin-angiotensin axis activity and therefore produce blood pressure control. ACE inhibitor use in patients with ESRD can sometimes prove an exacting proposition. ACE inhibitors are variably dialysed, with compounds such as catopril, enalapril, lisinopril and perindopril undergoing substantial cross-dialyser clearance during a standard dialysis session. This phenomenon makes the selection of a dose and the timing of administration for an ACE inhibitor a complex issue in patients with ESRD. Furthermore, ACE inhibitors are recognised as having a range of nonpressor effects that are pertinent to patients with ESRD. Such effects include their ability to decrease thirst drive and to decrease erythropoiesis. In addition, ACE inhibitors have a unique adverse effect profile. As is the case with their use in patients without renal failure, use of ACE inhibitors in patients with ESRD can be accompanied by cough and less frequently by angioneurotic oedema. In the ESRD population, ACE inhibitor use is also accompanied by so-called anaphylactoid dialyser reactions. Angiotensin antagonists are similar to ACE inhibitors in their mechanism of blood pressure lowering. Angiotensin antagonists are not dialysable and therefore can be distinguished from a number of the ACE inhibitors. In addition, the adverse effect profile for angiotensin antagonists is remarkably bland, with cough and angioneurotic oedema rarely, if ever, occurring. In patients with ESRD, angiotensin antagonists are also not associated with the anaphylactoid dialyser reactions which occur with ACE inhibitors. The nonpressor effects of angiotensin antagonists--such as an influence on thirst drive and erythropoiesis--have not been explored in nearly the depth, as they have

been with ACE inhibitors. Although ACE inhibitors have not been compared directly to angiotensin antagonists in patients with ESRD, angiotensin antagonists possess a number of pharmacokinetic and adverse effect characteristics, which would favour their use in this population.

L6 ANSWER 56 OF 166 MEDLINE on STN
ACCESSION NUMBER: 2000349404 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10889139
TITLE: Reverse remodeling of cardiac myocyte hypertrophy in hypertension and failure by targeting of the renin-angiotensin system.
AUTHOR: Tamura T; Said S; Harris J; Lu W; Gerdes A M
CORPORATE SOURCE: South Dakota Health Research Foundation, Cardiovascular Research Institute, Sioux Falls, SD 57105, USA.
CONTRACT NUMBER: HL-30696 (NHLBI)
SOURCE: Circulation, (2000 Jul 11) Vol. 102, No. 2, pp. 253-9.
Journal code: 0147763. E-ISSN: 1524-4539.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 11 Aug 2000
Last Updated on STN: 21 May 2001
Entered Medline: 1 Aug 2000
AB BACKGROUND: ACE inhibitors (ACEIs) and angiotensin II type 1 (AT(1)) receptor blockers are effective in reducing left ventricular mass in hypertension and heart failure. However, the ability of these drugs to reverse excessive myocyte lengthening and transverse growth in heart failure is unknown. METHODS AND RESULTS: L-158,809 (an AT(1) blocker; AT(1)), enalapril (an ACEI), and hydralazine (a vasodilator) were administered to spontaneously hypertensive heart failure rats between 6 and 10 months of age (early treatment) and between 18 and 22 months of age (late treatment). After 4 months of treatment, hemodynamics and chamber dimensions were collected before left ventricular myocyte isolation and subsequent analysis of myocyte shape. Each drug reduced systolic blood pressures to normal values. In the early and late studies, the ACEI reduced myocyte volume. Myocyte length was also reduced in the late study. However, the AT(1) was most effective in reversing myocyte dimensions to near-normal values in both studies. Hydralazine was ineffective in reducing cell size but arrested progression of myocyte lengthening in the late study. Changes in myocyte shape reflected alterations in chamber dimensions and wall thickness. CONCLUSIONS: Reversal of myocyte hypertrophy was produced in hypertensive/heart failure rats with an AT(1). The ACEI was effective but to a lesser extent. Results indicate that it is possible to significantly reverse myocyte remodeling pharmacologically even if therapy is initiated near the onset of failure. Further work is needed to determine whether similar results can be obtained in humans.

L6 ANSWER 57 OF 166 MEDLINE on STN
ACCESSION NUMBER: 2000283788 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10822316
TITLE: Haemorheological effects of losartan and enalapril in patients with renal parenchymal disease and hypertension.
AUTHOR: Shand B I
CORPORATE SOURCE: Department of Nephrology, Christchurch Hospital, Christchurch, New Zealand.
SOURCE: Journal of human hypertension, (2000 May) Vol. 14, No. 5, pp. 305-9.
Journal code: 8811625. ISSN: 0950-9240.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: (CLINICAL TRIAL)

Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 6 Jul 2000
Last Updated on STN: 6 Jul 2000
Entered Medline: 23 Jun 2000

AB The objective of this study was to compare the effects of the angiotensin II (ang II) antagonist, losartan and the angiotensin-converting enzyme inhibitor (ACEI), enalapril on haemorheology.
Twenty-nine patients with renal parenchymal disease and hypertension were enrolled in the prospective, open, parallel study that involved a 14-day washout period followed by a 120-day treatment period. Patients were allocated randomly to receive either losartan 50-100 mg/day (n = 15) or enalapril 2.5-10 mg/day (n = 14) to achieve blood pressure control <140/90 mm Hg. Blood pressure, haemorheology profile and plasma fibrinogen concentration were measured after the washout phase and after 2, 10, 60, and 120 days of treatment. The data were analysed using ANOVA with repeated measures. Twenty-seven patients completed the study. Treatment with both losartan and enalapril was associated with a significant decrease ($P < 0.05$) in relative high shear rate whole blood viscosity, indicating an increase in blood cell deformability. In patients taking losartan, the increase in blood cell deformability did not result in a decrease in mean whole blood viscosity due to a concomitant, significant increase in mean plasma viscosity ($P < 0.01$). In contrast, the improved cell deformability in patients treated with enalapril resulted in a small and statistically insignificant decrease in mean whole blood viscosity ($P = 0.06$; mean change = -0.15 mPa sec). The mechanism of the increase in blood cell deformability and the rise in plasma viscosity associated with losartan remain unclear. It is possible but unproven that the improvement in intrinsic blood cell rheology with losartan and enalapril may be the result of changes in cation transport systems and/or the consequence of the protective antioxidant properties of drug metabolites.

L6 ANSWER 58 OF 166 MEDLINE on STN
ACCESSION NUMBER: 2000244493 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10783907
TITLE: Enalapril in subantihypertensive dosage attenuates kidney proliferation and functional recovery in normotensive ablation nephropathy of the rat.
AUTHOR: Krivosikova Z; Sebekova K; Spustova V; Lajdova I; Dzurik R
CORPORATE SOURCE: Institute of Preventive and Clinical Medicine, Bratislava, Slovak Republic.. krivosikova@upkm.sk
SOURCE: Physiological research / Academia Scientiarum Bohemoslovaca, (1999) Vol. 48, No. 6, pp. 429-35.
Journal code: 9112413. ISSN: 0862-8408.
PUB. COUNTRY: Czech Republic
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200005
ENTRY DATE: Entered STN: 25 May 2000
Last Updated on STN: 25 May 2000
Entered Medline: 18 May 2000

AB Most studies on the antiproliferative action of angiotensin converting enzyme inhibitors (ACEI) were performed in a rat hypertensive remnant kidney model with 5/6 kidney ablation which raised objections about the antihypertensive effect of ACEI and the influence of other antihypertensive drugs administered to remnant kidney control rats. To prevent these objections, a normotensive 4/6 remnant kidney model was elaborated and a subantihypertensive dosage of enalapril was used to evaluate its

antiproliferative action. Subtotally nephrectomized rats (Nx) markedly increased the remnant kidney weight during a 4-week period and this rise was prevented by the treatment with enalapril (NxE) (Nx +297+/-35 mg vs. sham-operated +145+/-32 mg, p<0.001; NxE +154+/-35 mg vs. Nx p<0.001). While collagen concentration in the kidney cortex was not increased in sham-operated rats (Sham) in comparison with the control group (Ctrl) at the beginning of the study, the subsequent increase was significant in the Nx group and enalapril did not attenuate this increase (Sham 148+/-5 mg/100 g w.w. vs. Nx 164+/-2 mg/100 g w.w., p<0.01; NxE 161+/-4 mg/100 g w.w. vs. Sham p<0.05). The tubular protein/DNA ratio increase, which was significant in the Nx group, was inhibited by enalapril (Nx 26.2+/-10.5 vs. NxE 15.3+/-2.6, p<0.05). The protein/DNA ratio was much lower in glomeruli, with no significant changes in either the Nx or NxE groups. Serum urea concentrations were slightly higher in the Nx group than in the sham-operated group, but markedly elevated in the NxE group (Nx 10.71+/-0.76 mmol/l vs. Sham 6.10+/-0.33 mmol/l, p<0.001; NxE 28.9+/-2.6 mmol/l vs. Sham p<0.001). Creatinine concentrations in the Nx group were increased in comparison with the sham-operated group and markedly increased in the NxE group (Nx 63.7+/-3.56 micromol/l vs. Sham 37.2+/-2.84 micromol/l, p<0.001; NxE 107.0+/-5.2 micromol/l vs. Sham p<0.001). The clearance of creatinine was lower in the Nx group than in the sham-operated group and was markedly reduced in the NxE group (Nx 0.89+/-0.06 ml/min.g kidney weight vs. Sham 1.05+/-0.16 ml/min x g kidney weight, p<0.01; NxE 0.58+/-0.029 ml/min x g kidney weight vs. Sham, p<0.001). Enalapril improved proteinuria in comparison with the Nx group (NxE 5.6+/-0.6 mg/24 h vs. Nx 16.1+/-3.4 mg/24 h, p<0.05). Thus remnant kidney proliferation is substantial even in normotensive rats. It includes both proliferation and collagen accumulation with partial recovery of kidney weight and function, but is accompanied by enhanced proteinuria. Enalapril attenuates the proliferation and decreases proteinuria but prolongs kidney function recovery.

L6 ANSWER 59 OF 166 MEDLINE on STN
ACCESSION NUMBER: 2000235125 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10775055
TITLE: Effects of short-term glycemic control, low protein diet and administration of enalapril on renal hemodynamics and protein permselectivity in type 2 diabetic patients with microalbuminuria.
AUTHOR: Narita T; Koshimura J; Suzuki K; Murata M; Meguro H; Fujita H; Kitazato H; Ito S
CORPORATE SOURCE: Division of Geriatric Medicine, Akita University Hospital, Japan.. narita@med.akita-u.ac.jp
SOURCE: The Tohoku journal of experimental medicine, (1999 Oct) Vol. 189, No. 2, pp. 117-33.
Journal code: 0417355. ISSN: 0040-8727.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 29 Jun 2000
Last Updated on STN: 29 Jun 2000
Entered Medline: 21 Jun 2000

AB To determine whether each of glycemic control (GC), low protein diet (LPD) or administration of angiotensin converting enzyme inhibitor (ACEI) has beneficial effects on diabetic nephropathy through the different mechanisms, changes in charge and size selectivity of glomerulus and renal hemodynamics were analyzed in microalbuminuric type 2 diabetic patients after additive combination therapy (first period: GC only, second period: GC-LPD, third period: GC+LPD+ACEI). To detect improvement of the impairments of glomerular charge selectivity and

size selectivity, changes in the ratio of the renal clearance of two plasma proteins with similar molecular radii and different isoelectric points (pIs) (ceruloplasmin and IgG: CRL/IgG) and changes in the ratio of the renal clearance of two plasma proteins with similar pIs and different molecular radii (alpha2-macroglobulin and albumin: alpha2/Alb) were examined before and after each therapy. Creatinine clearance decreased significantly in the first and third periods although slight but not significant decrease was detected in the second period. Filtration fraction was significantly decreased only in the third period. Although renal clearances of Alb, IgG and CRL were decreased in periods of all three therapies, that of alpha2-macroglobulin with a large molecular radius was decreased significantly only after the third therapy. Neither CRL/IgG nor alpha2/Alb changed during these three therapies. These findings suggest that each of three short-term therapies consisting of GC, GC+LPD and GC+LPD+ACEI, reduced proteinuria in microalbuminuric type 2 diabetic patients not through the improvement of renal size and charge selectivities, but through improvement of renal hemodynamics.

=> dis ibib abs l6 40-49

L6 ANSWER 40 OF 166 MEDLINE on STN
ACCESSION NUMBER: 2002648432 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12407639
TITLE: Dynamic renal blood flow measurement by positron emission tomography in patients with CRF.
AUTHOR: Juillard Laurent; Janier Marc F; Fouque Denis; Cinotti Luc; Maakel Nora; Le Bars Didier; Barthez Paul Y; Pozet Nicole; Laville Maurice
CORPORATE SOURCE: Hospices Civils de Lyon, France.. laurent.juillard@chu-lyon.fr
SOURCE: American journal of kidney diseases : the official journal of the National Kidney Foundation, (2002 Nov) Vol. 40, No. 5, pp. 947-54.
Journal code: 8110075. E-ISSN: 1523-6838.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200212
ENTRY DATE: Entered STN: 5 Nov 2002
Last Updated on STN: 17 Dec 2002
Entered Medline: 4 Dec 2002

AB BACKGROUND: Positron emission tomography (PET) is a functional imaging device that allows dynamic regional blood flow measurements. We performed a study to test whether PET could detect acute changes in renal blood flow (RBF) in patients with chronic renal failure (CRF). METHODS: RBF was measured by means of PET (PET-RBF) using oxygen 15-labeled water (H2(15)O) in eight men with hypertension and moderate CRF before and 5, 40, 80, and 120 minutes after the injection of quinaprilat (10 mg intravenously). Effective renal plasma flow (ERPF) and glomerular filtration rate (GFR) were measured simultaneously by para-aminohippuric acid (PAH-ERPF) and inulin clearances before and 20, 60, 100, and 140 minutes after quinaprilat injection. RESULTS: Baseline RBF and ERPF were decreased in all patients (221 +/- 20 mL/min/100 g and 225 +/- 38 mL/min/1.73 m2, respectively). PET-RBF increased significantly after quinaprilat injection (+15%, +26%, +19%, and +23% versus baseline; P < 0.003). PAH-ERPF did not increase significantly (-6%, +12%, +20%, and +15% versus baseline; P = 0.15). GFR (50.1 +/- 8.9 mL/min/1.73 m2 at baseline) did not change significantly after quinaprilat injection; however, filtration fraction (GFR-ERPF ratio) decreased significantly from 0.23% +/- 0.02% to 0.20% +/- 0.02% (P = 0.0004). Mean arterial pressure decreased

significantly after quinaprilat injection (P < 0.005).
CONCLUSION: This study dynamically measured RBF by means of PET in patients with CRF for the first time. It showed that RBF rapidly increased after quinaprilat injection. PET using H2(15)O is a powerful method for the noninvasive measurement of dynamic changes in RBF that remain undetected by PAH clearance.

L6 ANSWER 41 OF 166 MEDLINE on STN
ACCESSION NUMBER: 2002425905 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12182524
TITLE: Using ACE inhibitors appropriately.
AUTHOR: Bicket Daphne P
CORPORATE SOURCE: Family Practice Residency Program, University of Pittsburgh Medical Center-McKeesport, Pennsylvania 15132, USA.. bicketdp@msx.upmc.edu
SOURCE: American family physician, (2002 Aug 1) Vol. 66, No. 3, pp. 461-8. Ref: 31
Journal code: 1272646. ISSN: 0002-838X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200208
ENTRY DATE: Entered STN: 17 Aug 2002
Last Updated on STN: 28 Dec 2002
Entered Medline: 30 Aug 2002
AB When first introduced in 1981, angiotensin-converting enzyme (ACE) inhibitors were indicated only for treatment of refractory hypertension. Since then, they have been shown to reduce morbidity or mortality in congestive heart failure, myocardial infarction, diabetes mellitus, chronic renal insufficiency, and atherosclerotic cardiovascular disease. Pathologies underlying these conditions are, in part, attributable to the renin-angiotensin-aldosterone system. Angiotensin II contributes to endothelial dysfunction. altered renal hemodynamics, and vascular and cardiac hypertrophy. ACE inhibitors attenuate these effects. Clinical outcomes of ACE inhibition include decreases in myocardial infarction (fatal and nonfatal), reinfarction, angina, stroke, end-stage renal disease, and morbidity and mortality associated with heart failure. ACE inhibitors are generally well tolerated and have few contraindications. (Am Fam Physician 2002;66:473.)

L6 ANSWER 42 OF 166 MEDLINE on STN
ACCESSION NUMBER: 2002372728 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11021187
TITLE: [Diabetic nephropathy with nephrotic syndrome--apropos of 2 cases. Advantages of combined conversion enzyme inhibitor and non-dihydropyridine calcium antagonist treatment]. Nephropathie diabetique avec syndrome nephrotique--a propos de deux cas. Avantages de l'association d'un inhibiteur de l'enzyme de conversion et d'un antagoniste du calcium non dihydropyridinique.
AUTHOR: Guelpa G
CORPORATE SOURCE: Hopital de la Providence, Service de medecine, Neuchatel.
SOURCE: Schweizerische Rundschau fur Medizin Praxis = Revue suisse de medecine Praxis, (2000 Aug 24) Vol. 89, No. 34, pp. 1331-8.
Journal code: 8403202. ISSN: 1013-2058.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: (CASE REPORTS)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: French

FILE SEGMENT: Priority Journals
ENTRY MONTH: 200207
ENTRY DATE: Entered STN: 17 Jul 2002
Last Updated on STN: 1 Aug 2002
Entered Medline: 31 Jul 2002

AB The inhibitors of the angiotensin-converting-enzyme (ACEI) are considered as the best pharmacological class for the treatment of patients with diabetic nephropathy. Independently of lowering the arterial blood pressure they reduce the proteinuria and slow the evolution of the renal failure. Calcium-channels blockers not belonging to the dehydropyridine-type (verapamil-diltiazem) possess some of these features, too, contrarily to the rest of calcium-antagonists (nifedipine-like). Two clinical studies dealing with type-II diabetic-patients whose nephropathy was complicated by a nephrotic syndrome and a rapid progressive renal failure showed that the combination of verapamil with an ACEI, further dietetic measures (protein restriction, saltless diet), permitted a significant decrement of the proteinuria as well as a stabilisation of the kidney function. This effect could not be shown under treatment with only ACEI. Thus the proteinuria-inhibiting and kidney-protecting effects of the combination of theses two substances-groups should be known when the physician is confronted at this clinical situation that determines the prognostic of the kidney function in such a dramatic way and short laps of time.

L6 ANSWER 43 OF 166 MEDLINE on STN
ACCESSION NUMBER: 2002368686 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12113190
TITLE: Taking ACE inhibitors during pregnancy. Is it safe?.
AUTHOR: Ratnapalan Savithiri; Koren Gideon
CORPORATE SOURCE: Hospital for Sick Children, Toronto, Ont.
SOURCE: Canadian family physician Medecin de famille canadien, (2002 Jun) Vol. 48, pp. 1047-9. Ref: 18
Journal code: 0120300. ISSN: 0008-350X.
PUB. COUNTRY: Canada
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200208
ENTRY DATE: Entered STN: 13 Jul 2002
Last Updated on STN: 30 Aug 2002
Entered Medline: 29 Aug 2002

AB QUESTION: A pregnant patient is taking enalapril for primary hypertension. How safe are angiotension-converting enzyme inhibitors (ACEI) during pregnancy? ANSWER: Evidence of whether ACEIs cause problems during the first trimester of pregnancy is reassuring. There is evidence that they cause severe renal and other problems during the second and third trimesters, however. These drugs should be avoided during pregnancy.

L6 ANSWER 44 OF 166 MEDLINE on STN
ACCESSION NUMBER: 2002196782 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11929321
TITLE: Clinical pharmacokinetics and selective pharmacodynamics of new angiotensin converting enzyme inhibitors: an update.
AUTHOR: Song Jessica C; White C Michael
CORPORATE SOURCE: Drug Information Center, Hartford Hospital, Hartford, Connecticut 06102-5037, USA.
SOURCE: Clinical pharmacokinetics, (2002) Vol. 41, No. 3, pp. 207-24. Ref: 98
Journal code: 7606849. ISSN: 0312-5963.
PUB. COUNTRY: New Zealand
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200206
ENTRY DATE: Entered STN: 4 Apr 2002
Last Updated on STN: 20 Jun 2002
Entered Medline: 19 Jun 2002

AB The angiotensin converting enzyme (ACE) inhibitors are widely used in the management of essential hypertension, stable chronic heart failure, myocardial infarction (MI) and diabetic nephropathy. There is an increasing number of new agents to add to the nine ACE inhibitors (benazepril, cilazapril, delapril, fosinopril, lisinopril, pentopril, perindopril, quinapril and ramipril) reviewed in this journal in 1990. The pharmacokinetic properties of five newer ACE inhibitors (trandolapril, moexipril, spirapril, temocapril and imidapril) are reviewed in this update. All of these new agents are characterised by having a carboxyl functional groups and requiring hepatic activation to form pharmacologically active metabolites. They achieve peak plasma concentrations at similar times (t(max)) to those of established agents. Three of these agents (trandolapril, moexipril and imidapril) require dosage reductions in patients with renal impairment. Dosage reductions of moexipril and temocapril are recommended for elderly patients, and dosages of moexipril should be lower in patients who are hepatically impaired. Moexipril should be taken 1 hour before meals, whereas other ACE inhibitors can be taken without regard to meals. The pharmacokinetics of warfarin are not altered by concomitant administration with trandolapril or moexipril. Although imidapril and spirapril have no effect on digoxin pharmacokinetics, the area under the concentration-time curve of imidapril and the peak plasma concentration of the active metabolite imidaprilat are decreased when imidapril is given together with digoxin. Although six ACE inhibitors (captopril, enalapril, fosinopril, lisinopril, quinapril and ramipril) have been approved for use in heart failure by the US Food and Drug Administration, an overview of 32 clinical trials of ACE inhibitors in heart failure showed that no significant heterogeneity in mortality was found among enalapril, ramipril, quinapril, captopril, lisinopril, benazepril, perindopril and cilazapril. Initiation of therapy with captopril, ramipril, and trandolapril at least 3 days after an acute MI resulted in all-cause mortality risk reductions of 18 to 27%. Captopril has been shown to have similar morbidity and mortality benefits to those of diuretics and beta-blockers in hypertensive patients. Captopril has been shown to delay the progression of diabetic nephropathy, and enalapril and lisinopril prevent the development of nephropathy in normoalbuminuric patients with diabetes. ACE inhibitors are generally characterised by flat dose-response curves. Lisinopril is the only ACE inhibitor that exhibits a linear dose-response curve. Despite the fact that most ACE inhibitors are recommended for once-daily administration, only fosinopril, ramipril, and trandolapril have trough-to-peak effect ratios in excess of 50%.

L6 ANSWER 45 OF 166 MEDLINE on STN
ACCESSION NUMBER: 2002054386 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11780954
TITLE: Enalapril: pharmacokinetic/dynamic inferences for comparative developmental toxicity. A review.
AUTHOR: Tabacova S A; Kimmel C A
CORPORATE SOURCE: National Center for Toxicological Research, US Food and Drug Administration, Rockville, MD 20857, USA.. STabacova@nctr.fda.gov
SOURCE: Reproductive toxicology (Elmsford, N.Y.), (2001 Sep-Oct) Vol. 15, No. 5, pp. 467-78. Ref: 95
Journal code: 8803591. ISSN: 0890-6238.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200202
ENTRY DATE: Entered STN: 25 Jan 2002
Last Updated on STN: 15 Feb 2002
Entered Medline: 14 Feb 2002

AB Enalapril is an antihypertensive drug of the class of angiotensin-converting enzyme inhibitors (ACEI) used in pregnancy for treatment of pre-existing or pregnancy-induced hypertension. The use of ACE inhibitors (drugs that act directly on the renin-angiotensin system) during the second and third trimester of pregnancy in humans is associated with specific fetal and neonatal injury. The syndrome, termed "ACEI fetopathy" in humans, does not appear to have a similar counterpart in experimental animals. The present paper reviews pharmacokinetic and pharmacodynamic aspects of enalapril that are physiologically important during pregnancy and intrauterine development in humans and in experimental animal species with the aim of better understanding the comparability of the manifestations of enalapril developmental toxicity in animals and humans. The human fetus is at a disadvantage with regard to in utero enalapril exposure in comparison to some of the animal species for which gestational pharmacokinetic data are available. Important reasons for the higher vulnerability of the human fetus are its accessibility by enalapril and the earlier (relative to animal species) intrauterine development of organ systems that are specific targets of ACEI pharmacologic effect (the kidney and the renin-angiotensin system). In humans, these systems develop prior to calcarial ossification at the end of first trimester of pregnancy. The specific pharmacodynamic action of enalapril on these systems during fetal life is the chief determinant of the etiology and pathogenesis of ACEI fetopathy in humans. In contrast, in most of the studied animal species, these target systems are not developed until close to term when the fetus is relatively more mature (and therefore less vulnerable), so that the window of vulnerability is narrower in comparison to the human. Among animal species, the best concordance in fetal pharmacodynamics to the human is seen in the rhesus monkey, but further studies are necessary to determine if similar developmental pathology is induced in this animal model upon repeated administration of the drug during the relevant period of intrauterine development. Animal-human concordance of developmental toxicity is least likely in the rat because of greater disparities in enalapril availability to the fetus and the relative development of the kidney and skeletal ossification compared to that in humans.

L6 ANSWER 46 OF 166 MEDLINE on STN
ACCESSION NUMBER: 2002011422 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11388646
TITLE: Involvement of angiotensin II in progression of renal injury in rats with genetic non-insulin-dependent diabetes mellitus (Wistar fatty rats).
AUTHOR: Noda M; Matsuo T; Nagano-Tsuge H; Ohta M; Sekiguchi M; Shibouta Y; Naka T; Imura Y
CORPORATE SOURCE: Pharmacology Research Laboratories II, Takeda Chemical Industries, Ltd., Osaka, Japan.. Noda_Masakuni@takeda.co.jp
SOURCE: Japanese journal of pharmacology, (2001 Apr) Vol. 85, No. 4, pp. 416-22.
Journal code: 2983305R. ISSN: 0021-5198.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112

ENTRY DATE: Entered STN: 21 Jan 2002
Last Updated on STN: 13 Mar 2003
Entered Medline: 5 Dec 2001

AB Wistar fatty (WF) rats have a genetic predisposition to hyperglycemia, polyuria, hyperinsulinemia, hyperlipidemia, obesity and nephropathy. These phenotypic characteristics are similar to those observed in obese patients with non-insulin-dependent diabetes mellitus (NIDDM) nephropathy. In this study, the effects of two types of renin-angiotensin system inhibitors, an angiotensin II type 1-receptor antagonist (AT1A) and an angiotensin I-converting enzyme inhibitor (ACEI), on renal injury in WF rats were studied during the progressive phase of diabetic nephropathy. An AT1A, candesartan cilexetil (1 mg/kg), and an ACEI, enalapril (10 mg/kg), were administered orally once a day for 12 weeks, beginning when the rats were 27-week-old and already showed diabetic nephropathy and obesity. Both drugs prevented an increase in proteinuria during the experimental period. Furthermore, after 4-week intervention, the levels of proteinuria were markedly lower in drug-treated rats. At the end of the experiment, both drugs prevented the development of glomerular lesions without affecting glucose metabolism and obesity. In conclusion, the inhibition of angiotensin II activity ameliorated both existing proteinuria and the progression of proteinuria, resulting in preservation of glomerular structure. Thus angiotensin II plays important roles in the development and the progression of nephropathy in genetically obese diabetic WF rats.

L6 ANSWER 47 OF 166 MEDLINE on STN
ACCESSION NUMBER: 2002003331 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11752035
TITLE: Contribution of volume overload and angiotensin II to the increased pulse wave velocity of hemodialysis patients.
AUTHOR: Tycho Vuurmans J L; Boer Walther H; Bos Willem-Jan W; Blankestijn Peter J; Koomans Hein A
CORPORATE SOURCE: Department of Nephrology and Hypertension, University Medical Center, Utrecht, The Netherlands.
SOURCE: Journal of the American Society of Nephrology : JASN, (2002 Jan) Vol. 13, No. 1, pp. 177-83.
Journal code: 9013836. ISSN: 1046-6673.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
(CONTROLLED CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200202
ENTRY DATE: Entered STN: 2 Jan 2002
Last Updated on STN: 26 Feb 2002
Entered Medline: 25 Feb 2002

AB Aortic compliance is decreased in patients with end-stage renal disease. This malfunction contributes to high aortic systolic pressures and thus to the development of left ventricular hypertrophy. It was hypothesized that besides structural vascular changes, functional changes as a result of hypervolemia and increased vasoconstrictor activity, in particular angiotensin II, play a role in decreasing aortic compliance. Nineteen hemodialysis patients were studied before and 24 h after they had been dialyzed to dry weight. Applanation tonometry of peripheral arteries was used to estimate aortic pulse wave velocity (PWV), known to depend on aortic compliance, and aortic systolic pressure augmentation (augmentation index [Aix]). Predialysis aortic PWV was increased in the dialysis patients compared with matched healthy subjects (9.9 +/- 3.1 versus 7.5 +/- 1.1 m/s; $P < 0.05$). The AIx was also increased (35 +/- 6 versus 25 +/- 10; $P < 0.05$). Volume reduction with dialysis had no significant effect on PWV (9.3 +/- 1.5 m/s), but the AIx decreased (28 +/- 7; $P < 0.05$). A subset of 10 patients were restudied after 1 wk of angiotensin-converting enzyme inhibition (ACEi) with

enalapril 5 mg once daily. ACEi decreased both predialysis as postdialysis BP but had no effect on pulse pressure and heart rate, which remained elevated compared with healthy subjects. ACEi also decreased predialysis aortic PWV, from 11.0 +/- 3.5 to 9.1 +/- 2.1 m/s (P < 0.05) but had no significant effect on AIx. During treatment with ACEi, the same volume reduction with dialysis decreased aortic PWV further to 8.0 +/- 1.4 m/s (P < 0.05), a figure not different from PWV in healthy subjects. AIx decreased to an even slightly subnormal value (12 +/- 23; P < 0.05). It was concluded that volume overload and angiotensin II both contribute to elevated PWV and AIx in dialysis patients. Volume reduction and ACEi both improve the aortic PWV and AIx. Combined volume reduction and ACEi has an enhanced effect that, in the present patients, was so large that PWV and AIx were no longer elevated. Monitoring and correcting of arterial pressure waves is feasible and may be an important tool in the treatment of patients with end-stage renal disease.

L6 ANSWER 48 OF 166 MEDLINE on STN
ACCESSION NUMBER: 2001571893 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11679443
TITLE: Modulation of incipient glomerular lesions in experimental diabetic nephropathy by hypotensive and subhypotensive dosages of an ACE inhibitor.
AUTHOR: Fabris B; Candido R; Carraro M; Fior F; Artero M; Zennaro C; Cattin M R; Fiorotto A; Bortoletto M; Millevoi C; Bardelli M; Faccini L; Carretta R
CORPORATE SOURCE: Department of Medicina Clinica and Neurologia, University of Trieste, Italy.. fabris@fmc.univ.treiste.it
SOURCE: Diabetes, (2001 Nov) Vol. 50, No. 11, pp. 2619-24. Journal code: 0372763. ISSN: 0012-1797.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 29 Oct 2001
Last Updated on STN: 23 Jan 2002
Entered Medline: 7 Dec 2001

AB A glomerular permeability defect occurs early in the course of type 1 diabetes and precedes the onset of microalbuminuria and renal morphological changes. Recently, ACE inhibitors have been shown to prevent loss of glomerular membrane permselective function, but the mechanism of this nephroprotective effect is still being debated. The objective of the present study was to evaluate the effects of hypotensive and subhypotensive dosages of the ACE inhibitor quinapril ex vivo and of its active metabolite quinaprilat in vitro on the glomerular albumin permeability (P(alb)) defect in the early phases of experimental diabetes. For the ex vivo study, six groups of male Wistar rats were evaluated for 4 weeks. One group served as a nondiabetic control (C); the other five groups were rendered diabetic and included untreated diabetic rats (D) and diabetic rats receiving quinapril at the dosages of 5 (DQ1), 2.5 (DQ2), 1.25 (DQ3), and 0.625 (DQ4) mg. kg(-1). day(-1). Dosage-dependent effects of quinapril on systolic blood pressure and the glomerular filtration rate were observed. In contrast, control of P(alb) in isolated glomeruli exposed to oncotic gradients, proteinuria, and glomerular and tubular hypertrophy was obtained with subhypotensive dosages (DQ3 and DQ4 groups) of the ACE inhibitor. In the in vitro study, quinaprilat reduced P(alb) significantly in concentration ranges from 10(-6) to 10(-14) mol/l compared with results in control glomeruli. The effect on P(alb) may have occurred by mechanisms different from kidney ACE inhibitor. These study results indicated that ACE inhibitor treatment prevents the early onset of the P(alb) defect in experimental diabetes. This effect seemed to occur independently of systemic or glomerular hemodynamic changes and, at least partially, from

kidney ACE inhibition.

L6 ANSWER 49 OF 166 MEDLINE on STN
ACCESSION NUMBER: 2001435148 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11302410
TITLE: Slowing the progression of renal disease in diabetic patients.
AUTHOR: Vivian E M; Goebig M L
CORPORATE SOURCE: University of the Sciences in Philadelphia, Department of Pharmacy Practice and Pharmacy Administration, Philadelphia College of Pharmacy, PA 19104-4495, USA.. e.vivian@usip.edu
SOURCE: The Annals of pharmacotherapy, (2001 Apr) Vol. 35, No. 4, pp. 452-63. Ref: 53
Journal code: 9203131. ISSN: 1060-0280.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 6 Aug 2001
Last Updated on STN: 21 Jan 2002
Entered Medline: 2 Aug 2001

AB OBJECTIVE: To review recent clinical trials that evaluate the most appropriate therapeutic options for delaying the progression of nephropathy in type 2 diabetic patients. DATA SOURCES: Primary and review articles were retrieved through a MEDLINE search (January 1990-January 2000). STUDY SELECTION AND DATA EXTRACTION: All studies related to attenuating the progression of nephropathy in diabetic patients were evaluated and included in this review. DATA SYNTHESIS: Clinical trials with angiotensin-converting enzyme inhibitors (ACEI) have consistently demonstrated a decrease in the progression of renal disease in diabetic patients. The angiotensin-2 receptor blocker (ARB) losartan has been shown to reduce microalbuminuria to the same extent as the ACEI enalapril. The nondihydropyridine calcium-channel blockers (NCCBs) verapamil and diltiazem have also been shown to decrease urinary albumin excretion. Clinical literature suggests that if monotherapy with an ACEI or ARB does not provide an adequate response, an NCCB should be added to the regimen. CONCLUSIONS: ACEIs should be considered first-line therapy for diabetic patients with nephropathy. ARBs should be considered as an alternative for patients who are unable to tolerate an ACE inhibitor due to adverse effects. If blood pressure goals are not achieved with an ACEI or ARB, then the addition of an NCCB should be considered.

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L6 ANSWER 30 OF 166 MEDLINE on STN
ACCESSION NUMBER: 2003250726 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12774769
TITLE: Enalapril accelerates remodeling of the renal interstitium after release of unilateral ureteral obstruction in rats.
AUTHOR: Koo Ja Wook; Kim Youngki; Rozen Silvia; Mauer Michael
CORPORATE SOURCE: Department of Pediatrics, Sanggye Paik Hospital, Inje University, Seoul, Korea.
SOURCE: Journal of nephrology, (2003 Mar-Apr) Vol. 16, No. 2, pp. 203-9.
Journal code: 9012268. ISSN: 1121-8428.
PUB. COUNTRY: Italy
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 200308
ENTRY DATE: Entered STN: 31 May 2003
Last Updated on STN: 21 Aug 2003
Entered Medline: 20 Aug 2003

AB Complete ureteral obstruction in rats rapidly leads to renal interstitial expansion and fibrosis and this process is ameliorated by concomitant angiotensin converting enzyme inhibition (ACEI). However, models of intervention initiated after unilateral ureteral obstruction (UUO) release may be more analogous to human obstructive renal disease where treatment could more reasonably follow the discovery of obstructive uropathy as compared to models where treatment is initiated at the time of experimentally induced obstruction. We studied interstitial changes in rats before and after release of UUO and examined the effect of ACEI with 200mg/L of enalapril (E) in the drinking water on these changes. Rats were sacrificed after 10 (n=10) and 20 (n=10) days (D) of UUO or 10D after release of 10D of UUO (n=18). Eleven rats received E for 10D after UUO release. Cortical interstitial volume fraction [Vv(I/C)] measured by point counting was increased at 10D (0.32 +/- 0.05) and 20D (0.41 +/- 0.05) of UUO compared to contralateral and sham-operated kidneys (both 0.05 +/- 0.01, ANOVA, $p < 0.001$). Vv(I/C) 10D after release from 10D of UUO (0.26 +/- 0.04) was lower than that of 10D of UUO ($p<0.05$) and much lower than those with 20D of UUO ($p<0.001$). However, rats treated with E from the time of UUO release had lower Vv(I/C) (0.21 +/- 0.07) than UUO released E untreated rats ($p<0.05$). Release of UUO initiates regression of interstitial expansion in rats. ACEI with enalapril significantly accelerates reversal of interstitial expansion after UUO release. This could have important implications for treatment of obstructive nephropathy in humans.

L6 ANSWER 31 OF 166 MEDLINE on STN
ACCESSION NUMBER: 2003212788 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12733362
TITLE: The mechanism of protective effects of enalapril on experimental diabetic nephropathy of rats.
AUTHOR: Fu J; Tian H; Liang J
CORPORATE SOURCE: Department of Endocrinology, First Affiliated Hospital, WCUMS, Chengdu 610041, China.
SOURCE: Hua xi yi ke da xue xue bao = Journal of West China University of Medical Sciences = Huaxi yike daxue xuebao / [bian ji zhe, Hua xi yi ke da xue xue bao bian wei hui], (2001 Mar) Vol. 32, No. 1, pp. 80-2.
Journal code: 8609552. ISSN: 0257-7712.
PUB. COUNTRY: China
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Chinese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200306
ENTRY DATE: Entered STN: 8 May 2003
Last Updated on STN: 1 Jul 2003
Entered Medline: 30 Jun 2003

AB OBJECTIVE: To elucidate the mechanisms of renoprotective effects of ACEI on diabetic animals and patients. METHODS: STZ-induced diabetic rats were treated with Enalapril and the levels of urine protein, TGF-beta and AGEs in renal tissue were measured and compared. RESULTS: The results of TGF-beta quantitation and AGE fluorescence of Enalapril treatment group rats were the same as those of diabetic control rats. CONCLUSION: Suppression of TGF-beta overexpression or AGEs accumulation was not implicated in the mechanisms of renoprotective effects of ACEI.

L6 ANSWER 32 OF 166 MEDLINE on STN
ACCESSION NUMBER: 2003155770 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12657763
TITLE: An unusual case of neonatal anuria.

AUTHOR: Prasad N; Gulati S; Jain M; Tewari P
CORPORATE SOURCE: Department of Nephrology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Raebareli Road, Lucknow 226 014, India.
SOURCE: Indian pediatrics, (2003 Mar) Vol. 40, No. 3, pp. 258-60. Journal code: 2985062R. ISSN: 0019-6061.
PUB. COUNTRY: India
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200305
ENTRY DATE: Entered STN: 4 Apr 2003
Last Updated on STN: 8 May 2003
Entered Medline: 7 May 2003

AB Neonatal anuria is not an uncommon problem in neonates. Here, we report an unusual case of neonatal anuria due to renal tubular dysgenesis, secondary to the use of angiotensin converting enzyme inhibitor (ACEI) during pregnancy. ACEI remains one of the most commonly used antihypertensive drug at present. A greater awareness needs to be created in the medical fraternity especially among pediatricians, gynecologists and internists that ACE inhibitors should not be prescribed during any trimester of pregnancy.

L6 ANSWER 33 OF 166 MEDLINE on STN
ACCESSION NUMBER: 2003122552 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12635373
TITLE: [Undesirable effects and interaction to angiotensin converting enzyme inhibitors therapy]. Efecte indezirabile si interactiuni medicamentoase la tratamentul cu inhibitori de enzima de conversie a angiotensinei.
AUTHOR: Ionescu Simona Daniela; Sandru V; Leuciuc Elena; Manea Paloma; Burdujan Alina; Tovarnitchi Svetlana; Cosovanu A
CORPORATE SOURCE: Clinica a III-a Medicala Cardiologica I. Enescu, Facultatea de Medicina, Universitatea de Medicina si Farmacie Gr.T. Popa Iasi.
SOURCE: Revista medico-chirurgicala a Societa t ii de Medici s i Naturalis ti din Ias i, (2002 Jan-Mar) Vol. 106, No. 1, pp. 128-31. Journal code: 0413735. ISSN: 0300-8738.
PUB. COUNTRY: Romania
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Romanian
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200304
ENTRY DATE: Entered STN: 16 Mar 2003
Last Updated on STN: 19 Apr 2003
Entered Medline: 18 Apr 2003

AB By their intervention upon the mechanisms regulating the vascular tone, renal plasma flow and direct actions of chemical structures, angiotensin-converting enzyme (ACE) inhibitors may determine undesirable effects. These effects formed the object of a 5-year retrospective study (1995-1999) carried out at the IIIrd Medical Clinic of Iasi. During this interval ACE inhibitors were administrated to 2178 patients with hypertensive and coronary disorders or heart failure of various causes. Different generations of ACE inhibitors were used, but captopril, enalapril and lysinopril were the most commonly administered. Undesirable effects were recorded in 161 patients (7.3%). The following side-effects, single or associated, were recorded: 38 patients (23.6%) had increasing blood pressure proportional with ACEI dose, 80 patients (49.7%) had decreasing blood pressure at low doses ACEI , 23 patients (14.4%) had kidney failure, 2 patients (1.2%) had both increasing blood pressure and kidney failure, 3 patients (1.9%) had both decreasing blood pressure and kidney failure, 6

patients (3.8%) had dry cough, one patient (0.6%) had kidney failure with decrease blood pressure and allergic dermatitis, 4 patients (2.4%) had allergic dermatitis, and 4 patients (2.4%) had headache, vertigo, paresthesia. CONCLUSIONS: The treatment with ACE inhibitors has to be carefully initiated under strict clinical and biological monitoring, preferably in hospital setting. No drug associations that favor the undesirable effects of ACE inhibitors were reported.

L6 ANSWER 34 OF 166 MEDLINE on STN
ACCESSION NUMBER: 2003090672 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12602539
TITLE: Moexipril and quinapril inhibition of tissue angiotensin-converting enzyme activity in the rat: evidence for direct effects in heart, lung and kidney and stimulation of prostacyclin generation.
AUTHOR: Torsello A; Locatelli V; Cella S G; Sanguini A M; Berti F
CORPORATE SOURCE: Department of Experimental and Environmental Medicine and Biotechnology, University of Milan, Bicocca, Italy.. antonio.torsello@unimib.it
SOURCE: Journal of endocrinological investigation, (2003 Jan) Vol. 26, No. 1, pp. 79-83.
Journal code: 7806594. ISSN: 0391-4097.
PUB. COUNTRY: Italy
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200308
ENTRY DATE: Entered STN: 27 Feb 2003
Last Updated on STN: 12 Aug 2003
Entered Medline: 11 Aug 2003

AB The activation of angiotensin converting enzyme (ACE) may contribute to the development of vascular and myocardial structural changes. The level of ACE is stable in human plasma, and only limited data are available on its regulation at the tissue level. The aim of this study was to characterize the effects of two ACE inhibitors, moexipril and quinapril on tissue ACE activity. Adult male rats were treated intragastrically once daily for 6 days either with 2 mg/kg moexipril or quinapril. After single treatment, moexipril and quinapril effectively inhibited ACE activity in plasma and slightly in heart and aorta, whereas after 6 days of treatment they inhibited ACE activity in plasma (87% and 94%, respectively), lung (92% and 93%), myocardium (26% and 23%), kidney (21% and 20%), and aorta (39% and 40%), but not in skeletal muscle. Interestingly, the two ACE-inhibitors also induced a significant increase in cardiac homogenates of 6-keto-PGF1alpha levels, an important index of PGI2 generation. To test whether the reduced effects of ACE inhibitors in heart and kidney were caused by a limited availability of the drugs, 100 microl of lung, heart and kidney homogenates from control rats were incubated in vitro with moexipril and quinapril immediately before assay. Both drugs were more effective in lung than heart and kidney homogenates, with inhibition values superimposable to those obtained in vivo. These results clearly indicate that inhibition of tissue ACE activity does not depend primarily on the availability of ACE inhibitors in each organ.

L6 ANSWER 35 OF 166 MEDLINE on STN
ACCESSION NUMBER: 2003058913 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12569273
TITLE: Reduced activity of the kallikrein-kinin system predominates over renin-angiotensin system overactivity in all conditions of sodium balance in essential hypertensives and family-related hypertension.
AUTHOR: Sanchez Ramiro; Nolly Hector; Giannone Carlos; Baglivo Hugo P; Ramirez Agustin J

CORPORATE SOURCE: Seccion Hipertension Arterial, Instituto de Cardiologia y Circugia Cardiovascular, Fundacion Favaloro, Belgrano, Buenos Aires, Argentina.
SOURCE: Journal of hypertension, (2003 Feb) Vol. 21, No. 2, pp. 411-7.
Journal code: 8306882. ISSN: 0263-6352.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200310
ENTRY DATE: Entered STN: 6 Feb 2003
Last Updated on STN: 14 Oct 2003
Entered Medline: 13 Oct 2003

AB OBJECTIVE: To study the renin-angiotensin-aldosterone and kallikrein-kinin systems in essential hypertensives and offspring of hypertensive parents during different sodium loads, and to explore their possible influence on renal hemodynamics. METHODS: Forty-five essential hypertensives (35 +/- 4 years old, 25 males), 30 offspring of hypertensive parents (26 +/- 8 years old, 16 males) and 30 normotensive controls (28 +/- 5 years old, 20 males) were submitted to three different sodium loads (high, 250 mmol/l; normal, 140 mmol/l; and low, 20 mmol/l). Blood pressure, plasma renin activity, serum aldosterone, total kallikrein and urinary kallikrein-like activity were measured after each period. Effective renal plasma flow and glomerular filtration rate were also measured. In essential hypertensive subjects, renal hemodynamic and hormonal parameters were also measured after 3 days of 20 mg enalapril administration. RESULTS: Plasma renin activity and serum aldosterone were higher in normotensives, essential hypertensives and offspring of hypertensive parents only during low sodium intake, whereas urinary kallikrein activity was lower in hypertensive offspring and essential hypertensives, compared with normotensives, during the three diet conditions. Effective renal plasma flow was found to be reduced in hypertensives and normotensive offspring, while the glomerular filtration rated was similar in the three groups. Angiotensin converting enzyme inhibitor (ACEI) administration to essential hypertensives for 3 days normalized effective renal plasma flow, increased plasma renin activity and decreased aldosterone and urinary kallikrein activity. CONCLUSIONS: Our observations confirmed the presence of a hormonal imbalance between the renin-angiotensin-aldosterone system and the kallikrein-kinin system, not only in essential hypertensives but also in the offspring of hypertensive parents. This imbalance probably affects the renal circulation and sodium homeostasis, since there was reduced effective renal plasma flow in both populations compared with normotensive subjects. The positive effect of ACEI, resulting in normalization of the effective renal plasma flow in essential hypertensive patients, suggests the involvement of both systems in impaired renal circulation.

L6 ANSWER 36 OF 166 MEDLINE on STN
ACCESSION NUMBER: 2003031714 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12538086
TITLE: COX-2 inhibition potentiates the antiproteinuric effect of enalapril in uninephrectomized SHR.
AUTHOR: Harding Pamela; Glass William F 2nd; Scherer Steven D
CORPORATE SOURCE: Department of Pathology and Anatomy, Eastern Virginia Medical School, 700 Olney Road, Norfolk, VA 23501, USA.. hardinp@evmsmail.evms.edu
SOURCE: Prostaglandins, leukotrienes, and essential fatty acids, (2003 Jan) Vol. 68, No. 1, pp. 17-25.
Journal code: 8802730. ISSN: 0952-3278.
PUB. COUNTRY: Scotland: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 200404
ENTRY DATE: Entered STN: 23 Jan 2003
Last Updated on STN: 17 Dec 2003
Entered Medline: 26 Apr 2004

AB PGE(2) and PGI(2) reduce extracellular matrix deposition and their production is altered after ACE inhibitor (ACEi) treatment. We therefore hypothesized that cyclooxygenase (COX)-2 inhibition would exacerbate renal injury and antagonize the effects of ACEi. To test these hypotheses, WKY and SHR were uninephrectomized (UNX) and treated with either vehicle, enalapril , NS398 or enalapril+NS398. NS398 did not affect systolic blood pressure nor antagonize the antihypertensive effect of enalapril . Urinary protein excretion in UNX WKY was significantly decreased after treatment with either enalapril or NS398. In UNX SHR, enalapril reduced proteinuria, but NS398 alone had no effect. Administration of both drugs, however, further reduced proteinuria. In UNX WKY, treatment with either NS398 alone or both drugs reduced glomerular volume and similar results were observed in SHR. Surprisingly, these results disprove our original hypothesis and suggest that inhibition of COX-2 provides additional renoprotection to that of enalapril alone.

L6 ANSWER 37 OF 166 MEDLINE on STN
ACCESSION NUMBER: 2002738357 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12499886
TITLE: Captopril enhances transforming growth factor (TGF)-beta1 expression in peripheral blood mononuclear cells: a mechanism independent from angiotensin converting enzyme inhibition? A study in cyclosporine-treated kidney -transplanted patients.
AUTHOR: Di Paolo Salvatore; Schena Antonio; Stallone Giovanni; Grandaliano Giuseppe; Soccio Michela; Cerullo Giuseppina; Gesualdo Loreto; Paolo Schena Francesco
CORPORATE SOURCE: Department of Emergency and Organ Transplant, Division of Nephrology, University of Bari, Bari, Italy.. s.dipaolo@nephro.uniba.it
SOURCE: Transplantation, (2002 Dec 27) Vol. 74, No. 12, pp. 1710-5. Journal code: 0132144. ISSN: 0041-1337.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL) Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200301
ENTRY DATE: Entered STN: 28 Dec 2002
Last Updated on STN: 17 Jan 2003
Entered Medline: 16 Jan 2003

AB BACKGROUND: Angiotensin (Ang) II blockade has been shown to prevent the development of renal injury in immunologically mediated diseases, but the mechanism whereby it exerts its protective effect has not been clearly defined. Transforming growth factor (TGF)-beta1 is a multifunctional cytokine with a potent immunomodulatory activity that has the potential to counteract many of the pro-inflammatory effects apparently evoked by the activation of renin-angiotensin system (RAS) in immune cells. METHODS: We set up an ex vivo and in vitro model to evaluate the effect of the angiotensin converting enzyme inhibitor (ACEi) captopril on the gene and protein expression of TGF-beta1 in human peripheral blood mononuclear cells (PBMC). RESULTS: In 20 kidney transplant recipients chronically treated with cyclosporine (CsA), 1-month treatment with captopril increased TGF-beta mRNA by 120% and TGF-beta1 protein release by 140% upon stimulation of PBMC with phytohemagglutinin (PHA) and phorbol myristate acetate (PMA) (P<0.01). PBMC from healthy controls, when exposed in vitro to 5 microM captopril,

showed a significant increase of TGF-beta1 release, whereas the ACEi enalapril failed to modify the expression of the cytokine. Ang II (100 pM) strongly inhibited TGF-beta1 synthesis by PBMC, and such effect was completely abolished by the addition of 200 ng/mL CsA, as well as by 1 micrpM losartan. Thus, captopril enhances TGF-beta1 gene and protein expression by PBMC by way of a mechanism independent, at least in part, from ACE inhibition, while CsA abrogates the inhibition of TGF-beta1 expression induced by Ang II. CONCLUSION: Collectively, these findings support the utility of combined treatment with captopril and CsA in the multitherapeutic management of organ transplant and, possibly, a strategy to decrease the dose of the calcineurin inhibitor in kidney-transplant recipients.

L6 ANSWER 38 OF 166 MEDLINE on STN
ACCESSION NUMBER: 2002711475 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12473875
TITLE: Regression of ventricular and vascular hypertrophy: are there differences between structurally different angiotensin-converting enzyme inhibitors?.
AUTHOR: Raasch Walter; Bartels Torsten; Schwartz Christopher; Hauser Walter; Rutten Hartmut; Dominiak Peter
CORPORATE SOURCE: Institute of Experimental and Clinical Pharmacology and Toxicology, Medical University of Lubeck, Germany.. raasch@medinf.mu-luebeck.de
SOURCE: Journal of hypertension, (2002 Dec) Vol. 20, No. 12, pp. 2495-504.
Journal code: 8306882. ISSN: 0263-6352.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200306
ENTRY DATE: Entered STN: 17 Dec 2002
Last Updated on STN: 19 Jun 2003
Entered Medline: 18 Jun 2003

AB OBJECTIVES: It is well established that angiotensin-converting enzyme (ACE) inhibitors (ACEI) reduce blood pressure (BP) and hypertrophy of the left ventricle and vessels. The aim of our study was to compare chemically different ACEIs regarding their ability to modulate left ventricular and media hypertrophy, ACE activity and plasma endothelin-1 concentrations in spontaneously hypertensive rats (SHRs). DESIGN: After establishing equi-effective dose regimes, SHRs were treated (3 months) with captopril, enalapril, fosinopril or ramipril (2 x 25, 10, 20 or 1 mg/kg per day or corresponding 1% doses for studying blood pressure-independent effects). METHODS AND RESULTS: Systolic blood pressure was reduced in SHRs receiving high doses of captopril, enalapril, fosinopril or ramipril (-61, -54, -35 and -47 mmHg), whereas low doses were ineffective. Left ventricular weight was decreased in animals treated with high doses (captopril/enalapril /fosinopril/ramipril: -17/-19/-17/-19%), but not low doses of agents. Media thickness of thoracal aorta was reduced by administering high doses (captopril/enalapril/fosinopril/ramipril: -31/-32/-27/-26%) and low doses (-16/-22/-22/-19%) of agents. ACE activity was reduced in heart, aorta and kidney of rats treated with high and low doses of all ACE inhibitors, whereby high doses showed more pronounced effects. Plasma endothelin-1 concentrations were not altered. A blood-pressure-ineffective treatment with an AT -antagonist revealed similar effects on cardiovascular hypertrophy. CONCLUSIONS: ACEIs reduce cardiovascular hypertrophy uniformly via an AT -receptor- mediated mechanism, reinforcing the opinion that ACEI effects are indeed class effects. The significance of local renin-angiotensin systems was confirmed by antihypertrophic effects in the aorta that were apparent in the absence of any blood pressure reduction.

L6 ANSWER 39 OF 166 MEDLINE on STN
ACCESSION NUMBER: 2002673501 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12434137
TITLE: Effects of cyclooxygenase-2 (COX-2) inhibition on plasma and renal renin in diabetes.
AUTHOR: Komers Radko; Tian Wei; Lindsley Jessie N; Oyama Terry T; Cohen David M; Anderson Sharon
CORPORATE SOURCE: Division of Nephrology and Hypertension, Department of Medicine, Oregon Health and Science University, and the Portland Veterans Affairs Medical Center, 97201-2940, USA.
CONTRACT NUMBER: AG 14699 (NIA)
DK 52494 (NIDDK)
SOURCE: The Journal of laboratory and clinical medicine, (2002 Nov) Vol. 140, No. 5, pp. 351-7.
Journal code: 0375375. ISSN: 0022-2143.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200212
ENTRY DATE: Entered STN: 16 Nov 2002
Last Updated on STN: 17 Dec 2002
Entered Medline: 3 Dec 2002

AB COX-2-derived prostaglandins (PG) have been suggested to be important modulators of renin release and expression. However, the role of COX-2 in various high-renin states is still being debated. In the present studies we explored the role of COX-2-derived PG on basal and angiotensin converting enzyme inhibitor (ACEI)-stimulated plasma and renal renin concentrations (PRC and RRC, RIA), and mRNA expression (RmRNA, RNAse protection assay) in experimental diabetes (DM). Groups of moderately hyperglycemic (n = 5, approximately 350 mg/dl), streptozotocin-diabetic rats (D) after 3 weeks of DM were treated with a selective COX-2 inhibitor, MF-tricyclic (MF, 5 mg/kg/day for 10 days in food), the combination of MF and the ACEI enalapril (3 mg/kg/day), enalapril alone, or vehicle (MF-free chow), for 10 days. Non-diabetic control rats, fed MF-free chow, were also studied. All groups of diabetic rats demonstrated similar glycemic control. Treatment with ACEI resulted in significant elevations in PRC, RRC and RmRNA as compared to non-ACEI treated groups of diabetic and control rats. A similar rise in these parameters was observed in the rats treated with the combination of ACEI and MF. Furthermore, in diabetic rats treated with MF alone, PRC and RRC were similar to vehicle-treated animals. Diabetic rats demonstrated higher urinary PG as compared to controls. MF-treated rats demonstrated a significant reduction in urinary PG excretion. In summary, selective COX-2 inhibition influenced neither basal renin status nor ACEI-induced renin release and expression in diabetic rats. These findings do not support a significant role for COX-2 in mediating renin status in diabetes.